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OPHTHALMOSCOPY AND OPERATIONS FOR REDUCTION OF HIGH BLOOD PRESSURE

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ALBANY, N. Y.

HIGH blood pressure, a reflection of many underlying disease conditions, is prevalent and commonly fatal, but it is not in itself incompatible with a long and active life. The problem of caring for the afflicted has become so vital in the discussion of diagnosis and treatment that the literature on the subject is voluminous and repetition of outmoded methods for the recognition, alleviation and cure of this symptom frequently conceals the basic pathologic processes, without disclosing any beneficial therapy. In an aging population, in which the stresses and strains of life are increasingly evident in the violent conflicts of emotions and ideologies, the vascular system of man reflects the conditions under which he exists. In the medical world, this effect is most pronounced in what is designated as cardiovascular-renal disease.

The reactions to anxiety differ greatly. A given grade of vascular hypertension may produce a wide variety of symptoms and degrees of severity, more or less dependent on the age and sex, as well as on the peculiarities of the patient.

It has been well stated that "no one who has had any contact with hypertensive patients can escape the impression that heredity plays an important role in the production of high blood pressure." [1]

Perhaps few fields of ophthalmoscopic investigation have led to as many divergent, and sometimes contradictory, views as those concerned with "the fundus in hypertension." This lack of a uniform concept calls for simplification, rather than the advance of an elaborate system of grades. It is necesary to think of the pathologic changes in the fundus as a progressive process, neither constant as to duration nor regular in detail. If this is done, then a given pattern can be placed with some degree of accuracy as early or late, with the obvious intermediate gradations, or as rapid or slow in development. However, for this, a

Read at a meeting of the College of Physicians of Philadelphia, Section on Ophthalmology, Jan. 15, 1948.

1. O'Hare, J. P., and Walker, W. G.: Arteriosclerosis and Hypertension, Arch. Int. Med. **33**:343 (March) 1924.

thorough understanding and, above all, a competent recognition of the vessels of the fundus both in health and disease are prime requisites; parenthetically, it takes much time, critical inspection and a fine discriminating sense to differentiate correctly the physiologic from the pathologic signs.

Photographs of the fundus, when clear, sharply focused and including more than the nerve head and a small surrounding zone, supply information on which an elastic but uniform classification may be based.

Fralick and Peet [2] noted a frequent inability to differentiate angiospasm and early sclerosis of the retinal arteries. They stated the belief that the disappearance of the retinitis after lowering of the blood pressure through resection of the splanchnic nerves was evidence of an angiospastic, rather than an arteriosclerotic, lesion. They also stated that in most of their cases there was a combination of the two types. The more visible the sclerosis, the more difficult it was to demonstrate areas of localized angiospasm. They stated:

> If it is agreed that retinitis develops in areas in which there has been long-standing severe angiospasm, then the localized areas of retinitis, characterized by edema and hemorrhage, must be recognized as being associated with local spasms of the retinal arteries, even though masked by sclerosis.[2]

The authors made reference to rapidly progressive arteriolar nephrosclerosis ("malignant hypertension") and called attention to the ineffectual medical treatment.

Cohen [3] reported:

> Ophthalmoscopic diagnosis in cases of hypertensive disease requires a differentiation between arteriolar spasm and arteriolar sclerosis, which is an important but frequently impossible distinction.

Hallum [4] has recently suggested that when branches or portions of the arterioles show constriction without an increase, or indeed with a decrease, in the light reflex it is likely that angiospasm is present. Further, subsequent disappearance of these arteriolar constrictions is proof of their spastic nature, whereas if the constrictions persist or tend to increase permanent changes in the walls of the arterioles are indicated.

The opthalmoscopic reports are not numerous but express the views of the reporters.

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2. Fralick, F. B., and Peet, M. M.: Hypertensive Fundus Oculi After Resection of the Splanchnic Sympathetic Nerves, Arch. Ophth. **15**:840 (May) 1936.

3. Cohen, M.: Ophthalmoscopic Changes Associated with Hypertensive Vascular Disease as a Guide to Sympathectomy, Arch. Ophth. **37**:491 (April) 1947.

4. Hallum, A. V.: Changes in Retinal Arterioles Associated with the Hypertension of Pregnancy, Arch. Ophth. **37**:472 (April) 1947.

5. Footnote deleted by author.

A careful estimation of the grade of sclerotic changes in the retinal arterioles was suggested by McKeown.[6] Gans [7] proposed a classification with two parallel groups of signs: on one side, those emphasizing the sclerosis and, on the other, the arteriolar constriction, the retinopathy and the retinopathy with papilledema.

Friedenwald [8] called attention to the changes associated with senescence and concluded that in the early stages of hypertensive vascular disease without atherosclerosis the visible portions of the retinal arterial tree are either normal or, in some cases of the severest form, dilated, and he suggested that one should not overestimate the reliability of the ophthalmoscopic findings in the diagnosis of senescence.

He stated that many cases of atherosclerosis are uncomplicated by hypertension. In discussing the arteriolosclerotic process of hypertension, he stressed age and called attention to the fact that most patients with arteriosclerotic hypertension are over 60 and few under 50 years of age, whereas most of the patients with nonatherosclerotic hypertension have the onset of their hypertension under the age of 50 and have well developed signs of hyaline changes in the retinal arterioles before they reach 60. Patients under 40 or over 60 years of age present no serious difficulties in the differential diagnosis of these forms, but the 40 to 60 year age group represents an important fraction of the patients for whom the differential diagnosis must be made. He asserted that in patients over 60 with moderate, fixed hypertension the retinal vessels are almost always narrow and straight and branch at acute angles. There is a question in my mind whether the last statement is correct. It is certainly not borne out by my photographic records. More often than not, the vessels do not alter their course.

Tooke and Nicholls [9] stated:

> . . . by and large, this operation [splanchnectomy] is disappointing in its effect on the blood pressure level, but nevertheless, the patients are improved, when one takes into consideration symptoms and fundus findings.

A careful review of the published reports regarding surgical treatment leaves one in a state of confusion. This, however, is less marked if the perusal of papers is limited to those that have appeared in the past few years, in which, because of the more discriminating selection

6. McKeown, H. S.: Ocular Fundi in Essential Hypertension, Pre- and Post-Operative, New York State J. Med. **44**:2692 (Dec. 15) 1944.

7. Gans, J. A.: Classification of the Arteriosclerotic Hypertensive Fundus Oculi in Patients Treated with Sympathectomy, Arch. Ophth. **32**:267 (Oct.) 1944.

8. Friedenwald, J. S.: Disease Processes Versus Disease Pictures in Interpretation of Retinal Vascular Lesions, Arch. Ophth. **37**:403 (April) 1947.

9. Tooke, F. T., and Nicholls, J. V. V.: Changes in the Fundus Oculi Following Splanchnectomy for Malignant Hypertension, Canad. M. A. J. **41**:21 (July) 1939.

of patients and the more refined operative procedures, the results reported are more satisfactory to the patient and more satisfying to the surgeon.

If a complete physical examination reveals that the condition of the patient is favorable and if the findings in the fundus are to be the deciding factor for or against operation, the question is, "Are we as ophthalmologists prepared to give a detailed report of the ophthalmoscopic picture and, on the basis of that design, render a verdict for or against surgical intervention?" This responsibility is not only grave, but one calling for a high degree of knowledge and skill. This presentation emphasizes that the ophthalmoscopic picture is an important element in correctly estimating the advisability of a pressure-reducing operation.

At the beginning of any consideration of hyperpiesia it must be understood that the vast majority of patients with hypertension present no lesion of the fundus. This statement cannot be repeated too often. After a variable time, often several years, during which period the blood pressure may be extremely high, the earliest changes suggestive of hypertension appear. These signs are identical with those in the retinal vessels of elderly patients and consist in slight narrowing of the arteries with or without faint indentations of the veins where they are crossed by the arteries. The indentation of veins is not pathognomonic but only suggestive. Incidentally, it is time that the expression "nicking" be abolished as incorrect. Subsequently, there is an intensification of all signs, not a distinguishable stage, but an almost imperceptible accentuation, in which the arteries may become more tortuous in portions of the retinal tree or be limited to the macular region. Later, there are slightly increased arterial reflexes, elevations or compression of veins where they are crossed by the arteries and superficial streak hemorrhages. The vessels may be of uneven width and occasionally exhibit a genuine, visible spasm—contraction of one or more arteries. No exudates are present. Still later, the fundus signs are definitely those of retinopathy, with hemorrhages, exudates and increased involvement of the arteries. The pattern changes with time as a few exudates and large superficial hemorrhages appear, with marked increase in the light reflex from the arterial wall, a high grade of sclerosis, with white vessel walls, and deep indentations of the veins.

The nerve head may be swollen—papilledema. This mere statement is not sufficient, for the disk may not only be elevated but may have many new vessels on its surface and newly formed vessels in front of it, or it may be combined with hemorrhages in the vitreous, retinitis proliferans and adventitious new-formed vessels in the retina with large, pale areas of exudate or a macular star. In some cases the edema of

the nerve head may dominate the picture. This is indicative of increased intracranial pressure. To exclude an expanding growth may be so difficult that only by careful neurologic and roentgenographic examinations and a correlation of all the facts can a final opinion be rendered. It has been proved that retinal edema always precedes the macular star and that later the radiations of the star decrease in width and length until only a few small, radially arranged spots remain. Occasionally, if the patient lives long enough, even these disappear. The soft, gray retinal area, of variable size, commonly more or less rounded and overlying a retinal vessel, has been called a cotton wool patch. This sign is of great clinical significance, for it usually, although not invariably, indicates vascular deterioration. In some cases these alterations progress rapidly.

As the concluding phase of the disease is approached, more hemorrhages and more cotton wool patches appear; or neuroretinal edema with a macular star, detachment of the retina and other changes may develop.

Edema of the retina is commonly considered evidence of conversion from the benign to the terminal stage. It must be noted, however, that remissions can occur. Further, in many cases of the atherosclerotic type, a fulminating retinopathy never develops, but the patient dies of a cerebral or cardiac accident. Retinal hemorrhages, cotton wool spots and neuroretinal edema may be absorbed spontaneously. This possibility must constantly be kept in mind when one is evaluating therapeutic benefits. The importance of this warning is realized in the review of reports in which the disappearance of transitory signs is stressed as the direct result of operation. It is common knowledge that such signs frequently vanish without any medical treatment or surgical intervention.

Just when in this progressive disease should the ophthalmologist recommend operation, or even sanction it? If the surgeon concludes that the patient's condition warrants operation and the ophthalmologist has found no signs of retinopathy, there should be no delay. If the surgeon has decided to operate and asks only for a confirmatory opinion, the ophthalmologist will be derelict in his duty to the patient if, when he finds signs of fulminating retinopathy or papilledema, he does not report that there is little likelihood of prolonged benefit from operation. The obligation is of the utmost gravity and must be assumed if the patient who might be helped is to be given a chance, whereas the patient with terminal retinopathy is protected by his surgeon's vigorously opposing an operation.

Information of value may be gained from the observations presented in a few cases.

REPORT OF CASES

CASE 1.—A professional man aged 48 had, in 1941, normal fundi, with normal vision and a systolic pressure of 152 mm. Four years later, in 1945, without his having had any intercurrent infection, his systolic pressure was 220 mm., and he had one small, superficial retinal hemorrhage. A comparison of his fundus pictures showed little compression of veins and no visible alteration in the course or caliber of the retinal vessels.

Ten months later, his blood pressure was 245 systolic and 110 diastolic. Operation was performed by Dr. R. H. Smithwick in March 1945, first, on the right side and, two weeks later, on the left. The patient's physician, Dr. A. M. Yunich, reported: "On Oct. 26, 1945, he weighed 173 pounds (78.5 Kg.) and showed decided improvement, both mentally and physically. He had no complaints, and his blood pressure was 152 systolic and 90 diastolic when he was in the standing position without his belt. The urine had a specific gravity of 1.009 and was negative for albumin and sugar; microscopic examination revealed no abnormal constituents.

"On Jan. 30, 1946, the urine had a specific gravity of 1.015 but was otherwise not remarkable. The patient weighed 176 pounds (79.8 Kg.), and his general condition was excellent, even though his blood pressure had risen to 190 systolic and 100 diastolic.

"When last examined, in April 1947, he weighed 185 pounds (83.9 Kg.), and his general condition was remarkably good. He was working regularly and was in the best of spirits. He had no headache, dizziness, visual disturbances or precordial distress, such as he had been troubled with prior to operation. The most amazing clinical finding, however, was a rise in his blood pressure to the preoperative level of 210 systolic and 120 to 130 diastolic."

He was comfortable and was carrying on his professional activities. He had no retinal hemorrhages, and both the arteries and the veins were smaller than before operation. From the ophthalmoscopic standpoint, his was an excellent case for operation, for the changes in the retinal vessels were minimal.

CASE 2.—A married woman aged 29, on examination to determine the cause of pain in the occipital region, was found to have a systolic pressure of 200 mm.

The retina was clear, with no edema; the temporal half of the disk was flat; the nasal side was thick. The veins were slightly dilated throughout their course. The light reflex from the superior temporal artery was increased, and the width of the blood column was variable. In the left eye, the disk was outlined throughout its circumference; the retinal striations were defined; the veins were normal in size, and there was only slight narrowing of the arteries; many large vitreous reflexes partly concealed the vessels. The appearance of the fundi suggested hypertension.

Two years later, Dr. James L. Poppen saw the patient and made the following report:

"The average blood pressure was 240 systolic and 136 diastolic. There was no evidence of widespread vascular disease, although there was some decrease in renal function, as well as in the phenolsulfonphthalein output. The intravenous pyelograms were within normal limits. The urine concentrated to 1.026, with a slight trace of albumin; the nonprotein nitrogen measured 31 mg. per hundred cubic centimeters. The general blood picture was normal. Roentgenograms of the chest revealed only slight cardiac hypertrophy.

"On May 13, 1939, splanchnic resection, lumbar sympathectomy and nephroomentopexy were performed on the left side. On May 23, a splanchnicectomy,

subdiaphragmatic, and lumbar sympathectomy were executed on the right side. The patient had a right hemiplegia while in the hospital; this cleared up to some extent, but she was left with slight aphasia. Her blood pressure dropped considerably at this time, and within six months it was back to its usual level."

At this time the fundi showed no perceptible change except that the nasal side of the right disk was flatter than the temporal and the margin was visible. Five years later, the margin of the disk was perfectly distinct, the arteries were uniformly narrow and the veins were less distended.

At no time did the patient have any evidence of retinopathy. She had a cerebral accident and died July 20, 1945. For six years she was practically free from symptoms and carried on her usual household duties. Her fundi reflected this favorable outcome.

CASE 3.—F. H. was first examined on Oct. 18, 1943, at the age of 34. His complaint was difficulty in focusing for near work, and the only noteworthy item in his history was the occurrence of a cerebral hemorrhage in 1941, when his blood pressure was 270 mm. systolic.

Vision was 6/7.5 in each eye. The disks were clearly and distinctly outlined. There was some compression of the full retinal veins, and in the left eye a few round, granular retinal hemorrhages were noted.

In November 1943, Dr. David P. Boyd performed a Smithwick[10] transdiaphragmatic splanchnicectomy on the right side. The patient had a stormy convalescence, and the operation on the left side was not done until June 1944.

Dr. Boyd reported: "The patient's blood pressure showed a fair drop, although it fluctuated widely, at times being 140 and at others 210 mm., but never reaching the preoperative level. He had a smooth convalescence from the second operation."

The last photographs of the fundus were made on March 15, 1945, at which time there was a slight decrease in fulness of the veins and the arteries were narrower. Vision was 6/6 in each eye. In his latest report, of May 8, 1947, the patient stated: "I am feeling well. I have little trouble with my eyes; but it is rather difficult to concentrate, and my memory is poor." He has been fairly comfortable for four years.

CASE 4.—A woman, aged 40, in 1932 had frequent frontal headaches, which were most intense in the morning; she experienced considerable fatigue after reading and became sleepy on the least concentration on near work.

Vision in the right eye was 6/30 without glasses and 6/15 with correction. The fundus was normal, and the poor vision was the result of dense corneal opacities. Vision in the left eye was 6/6. The fundus was normal; the disk was sharply and clearly outlined, and the vessels were normal.

A year and a half later the headaches were said to be much worse. Physical examination revealed nothing significant except for the blood pressure, which was 180 systolic and 110 diastolic. The family physician placed her under medication. The fundi at this time showed slight narrowing of the retinal arteries and a faint haze in the retina.

She was not seen again until several years later, at which time the pressure was 240 systolic and 130 diastolic. There were marked irregularity in the caliber of the arteries, slight but measurable dilatation of the retinal veins and one streak hemorrhage. A splanchnicectomy was advised.

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10. Smithwick, R. H.: Surgery of the Sympathetic Nervous System, New England J. Med. **224**:329 (Feb. 20) 1941.

The following year, she had a Smithwick splanchnicectomy on the right side, and four months later a similar operation on the left side. After each operation she had pleurisy and an excessive amount of pain and was extremely uncomfortable and very short of breath. A year and a half later her fundi showed no notable change except that the superficial hemorrhage had disappeared.

Now, nearly two years after operation, she is still short of breath but has little headache and feels decidedly better, athough her pressure is stabilized at 200 systolic and 120 diastolic.

This case is one in which the ophthalmoscopic findings suggested a satisfactory result.

CASE 5.—A married woman aged 49, without general infection of any kind, had a systolic pressure of 218 mm., for relief of which she had been taking drugs for one month. Urinalysis and tests of renal function gave normal results. Her only complaint was pain in the left eye.

Vision in the right eye was 6/12 without correction, and 6/5 with a minus sphere. The retinal veins were uniformly dilated but not tortuous. The arteries were of uneven caliber and presented several frank spasms—contractions without evidence of changes in the vessel walls. There were increased tortuosity of the superior temporal artery; faint, but definite, retinal edema and a few round granular, deep retinal hemorrhages.

Vision in the left eye was 6/6. The disk was clearly outlined through slight retinal edema. The veins were straight and fuller than normal. The inferior branches of the arteries were tortuous. Several definite arterial spasms and some granular, deep red retinal hemorrhages and superficial streaks of blood were observed.

The patient had a bilateral Smithwick operation and died shortly thereafter.

In this case, the vascular changes were danger signs, the serious import of which should have been recognized and operation postponed indefinitely.

COMMENT

The majority of hypertensive patients are free from symptoms, and the high blood pressure is discovered on routine physical examination. The ophthalmologist often makes the original diagnosis of hypertension and inaugurates the investigations which may lead to an operation. The prime symptom for which he is consulted is an intense, persistent, treatment-resisting, generalized headache, or nuchal, occipital or frontal distress, frequently most intense in the early morning hours. Because of visual defects a patient may visit the ophthalmologist, who recognizes the causative significance of the vascular changes, the congestion of the fundus, the lack of retinal definition, the retinal hemorrhages, the retinopathy or the papilledema.

The ophthalmologist should be able to state with reasonable certainty whether a given fundus pattern indicates a favorable postoperative outcome, one of doubtful value or a disappointing result. He must know the life history of the retinal variations and estimate the life expectancy of the individual patient. He should render a concise, but genuinely explanatory, report, including an opinion based on knowledge of the favorable and unfavorable results following operation and on

understanding of the fundus signs. If this is done, more patients with a good prognosis will be operated on, and fewer of those with hopeless disease will be subjected to the trying ordeal, from which little or no benefit can be expected. The prognosis is based on the state of the retinal vessels.

The ophthalmoscopic signs which determine the feasibility of operation are correlated. Many exceptions may be made to them, and occasionally a patient with what seems to be a hopeless condition may, by operation, be given a few more years of life.

It must be remembered that hypertension is a complex manifestation of many factors, all of which must be evaluated before an accurate prognosis can be given. All advice is predicated on the integrity of the kidneys, the heart and the cerebral vessels.

From the ophthalmoscopic standpoint, there are two types of hypertension. In one there are very slight vascular changes, even after many years of high pressure. Eventually, the majority of patients die of a cerebral or cardiac accident without ever having had a retinopathy. The other, rapidly progressive arteriolar nephrosclerosis (so-called malignant hypertension), should be called fulminating because of the rapidly progressing retinopathy. Frequently, at the time of the initial examination, there are extensive exudates and hemorrhages, with or without retinal edema and an irregular outline of the blood column, spasm or white-walled sclerotic vessels. The fulminating type is comparatively seldom engrafted on the simple form of hypertensive vascular disease. There is, however, no definite duration of the benign stage and no reliable guide by which one can predict the imminence of the signs which almost invariably foretell an early death. It is to cases of this potentially fulminating type that the surgeon's attention is often directed, for without help the patient is doomed. As a last resort, an operation may be tried, for medical treatment is ineffective.

The severe cases of retinopathy are usually associated with signs of advanced renal dysfunction, so that the patient rarely reaches the standard of renal efficiency demanded by the most careful surgeons. Patients with papilledema and extensive neuropapillary edema should not be subjected to operation.

SUMMARY

If the patient has no serious involvement of the heart, kidneys or cerebral vessels and no retinopathy, the ophthalmologist can sanction operation.

If a retinopathy is present, with cotton wool patches, hemorrhages and exudates, approval may be given only when the results of physical and laboratory tests seem to warrant an operation, with the expectation that life will be lengthened.

If the patient has definite arteriosclerosis, as indicated by white-walled vessels; if he has round, deep, red, granular retinal hemorrhages; if there is considerable retinal edema, as evidenced by a decrease in the visibility of the retina, or if there are intense, widespread edema of the retina and obscuration of the margins of the disks, with or without newly formed vessels on or about the disk, operation is contraindicated. If he has had recent closure of a retinal artery, with the typical white edema in the region supplied by the closed vessel, or sudden occlusion of the central vein, operation should not be attempted.

If there is marked papilledema with narrowing of the arteries or fulness of the veins, operation should be opposed unless there are extenuating circumstances, at which time the surgeon assumes the responsibility and the patient understands the risks, for it is improbable that life will be materially prolonged by surgical intervention.

In addition to these sharply and clearly defined exceptions, there are many patients with little retinal edema, but with large, greatly indented veins and uneven lumen of the vessels. Such patients are poor risks.

Finally, if the patient with hypertension is to be made comfortable, his anxieties must be relieved and his fear of imminent disability or death dispelled.

344 State Street.

ELECTRONIC FLASH (GAS DISCHARGE) TUBE IN PHOTOGRAPHY OF THE ANTERIOR SEGMENT OF THE EYE

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AND
W. MORTON GRANT, M.D.
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SOME of the special requirements for illumination in photography of the anterior segment of the eye appear to be met more satisfactorily by a recently developed type of light source than by methods previously employed. For several reasons, in ocular photography it is expedient to have the camera relatively close to the eye. But the different distances of various structures of the eye, especially of its adnexa, from the camera make it necessary to use rather small lens apertures to obtain sharp definition. The small aperture of the diaphragm necessitates high levels of illumination for adequate exposure of the film.

With a lens aperture of f/2.8 a segment of the eye 5 mm. in depth is in fair focus, while with an aperture of f/16 a segment 20 mm. in depth is in comparable focus and the sharpness in the midrange is, of course, significantly improved. Because of the sensitivity of the eye to light and difficulty in holding the eye still, a short time of exposure must be employed to reduce discomfort and to "stop" any motion.

Two commonly employed sources of illumination for external ocular photography are flash bulbs, which contain combustible metal foil or wire, and overloaded incandescent filament lamps, commonly known as "photofloods." Flash bulbs give the necessary intense light, but are currently in short supply, are relatively expensive and must be replaced for each picture. Furthermore, an unpleasant blast of heat is felt by the patient when the flash bulb is placed in the photographically most desirable position. "Photofloods" are less satisfactory. Although they are frequently used in conjunction with a resistance, so that the camera may be focused in diminished light, in an attempt to lessen the patient's discomfort from heat and glare, the photophobic eye is still uncomfortable during focusing. Lacrimation is often excessive, producing highlights which detract from the picture. During exposure of the film, the resistance is removed by a switch, permitting the bulbs to

From the Howe Laboratory of Ophthalmology, Harvard University Medical School, and the Massachusetts Eye and Ear Infirmary.

light to their full brilliance; this flood of light is even more uncomfortable, and yet is of insufficient intensity to permit stopping down the lens adequately unless several lamps are used, with consequent increase in the number of corneal reflections.

Some of the defects of the illuminants already discussed have been overcome in a photographic arrangement utilizing an electronic flash (cold cathode gas discharge) tube. This tube contains one of the rare gases, which is caused to ionize by a high voltage discharge, producing light with a color temperature of about 6,500° K., suitable for use without filters with daylight "kodachrome" or "ansco" film. The flash is of high intensity but of brief duration, approximately 0.0001 second, and is remarkably cool, so that discomfort to the patient is at a minimum. The lacrimation and photophobia produced by "photofloods" and ordinary flash bulbs are notably absent.

The gas discharge tube has previously been used for ocular photography in an apparatus specially designed for photographing conjunctival and corneal vessels at considerable magnification.[1] While this apparatus is suitable for investigative work, a simpler arrangement, which may be used with ordinary types of cameras, is convenient for routine external ocular photography in the office or clinic. This arrangement can be operated quickly and easily by a nurse or secretary after a few minutes' instruction.

For use in routine photography of the anterior segment, the electronic flash tube is provided with a handle, reflector and a cone-shaped shield, as pictured in figures 1 and 2. A 75 watt, filament type projection bulb for illumination of the eye during focusing is mounted inside the shield, directly in front of the flash tube. At the small end of the cone is placed a piece of nearly colorless, heat-absorbing glass; this is not essential but adds to the patient's comfort by reducing to a minimum the heat from the projection bulb. The entire unit is flexibly supported alongside the camera, and as near to it as possible. The shield surrounding both lights serves to limit the emission of light to a beam only slightly larger than the desired photographic field. In this way, a spot of light is furnished from the continuously burning filament source, permitting accurate direction of the light toward the eye. When the discharge tube is flashed, the operator, patient and camera lens are protected from all light not actually directed at the eye to be photographed.

1. Gartner, S.: Blood Vessels of Conjunctiva: Studies with High Speed Macrophotography, Arch. Ophth. **32**:464 (Dec.) 1944. Pearce, cited by Tisdall, F. F.; McCreary, J. F., and Pearce, H.: The Effect of Riboflavin on Corneal Vascularization and Symptoms of Eye Fatigue in R. C. A. F. Personnel, Canad. M. A. J. **49**:5 (July) 1943.

Sufficient light to permit stopping down the camera lens to f/16 with color film is obtained when the flash tube is located 12 inches (30 cm.) from the eye (the small end of the cone is thus 4 inches [10 cm.] from the eye, or directly beside the camera lens) and is

Fig. 1.—Photograph of cone-shaped shield, containing focusing light in center, and electronic flash tube just in front of the reflector.

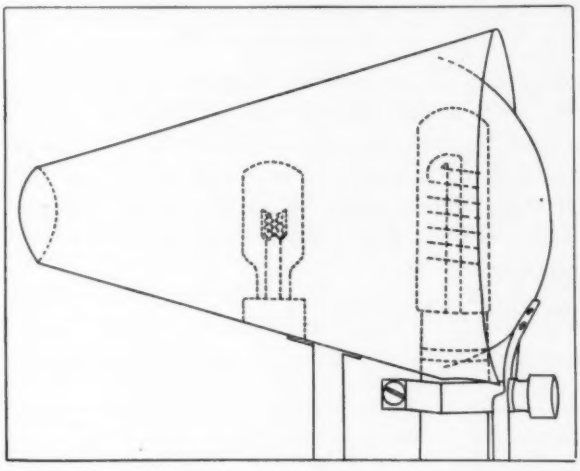

Fig. 2.—Schematic diagram of the apparatus shown in figure 1.

operated at maximum output by an appropriate power supply. It has been found satisfactory to employ flashes of an intensity of the order of 50,000,000 lumens and a total light output of 9,500 lumen seconds. For this purpose, the flash tube has been energized by a pair of 30 microfarad condensers, which are charged to 2,500 volts by a simple

transformer-rectifier circuit providing 200 watt seconds of energy per flash. Reputedly, the flash tube can be discharged at intervals of thirty seconds for more than 10,000 flashes. Electronic flash power supplies with characteristics similar to this laboratory-developed unit are available commercially.

No mechanical synchronization of the shutter with the flash is necessary, although this would be a convenience. The camera may simply be set on bulb, the shutter opened, the flash activated by pressing a small switch and the shutter closed. Depending on the speed of the operator's fingers, the shutter probably remains open upward of one-half second. Although the focusing lamp is permitted to burn continuously and the room is not darkened, this incidental illumination is of such relatively low intensity that it does not produce, either before or after the flash, any appreciable modification of the image recorded during the flash. The only perceptible image is recorded during the very brief flash, so that ocular motion does not interfere and blinking has been found to present no problem.

Experimental investigation of possible harmful effects to the eye from exposure to the electronic flash was carried out before its use on patients. Several volunteers were exposed to series of at least twenty flashes during ten to fifteen minutes. No discomfort or disturbance of vision was noted by them at any time after disappearance of the after-image of the light source.

SUMMARY

For photography of the anterior segment of the eye, an electronic flash tube of 9,500 lumen seconds' output provides more satisfactory illumination than the illuminants in common use for this purpose, permitting life-size color pictures to be taken at a desirably small lens aperture, yet with relatively little discomfort to the subject. A special flash tube holder, with an additional filament source for focusing, facilitates the procedure.

243 Charles Street (14).

ESTHETIC CORRECTION OF UNILATERAL ANOPHTHALMOS BY OPHTHALMOPROSTHESIS

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ANOPHTHALMOS was defined clinically by Mann [1] as a condition in which no eyeball, however small, can be found in the orbit. In life it would obviously be impractical to distinguish between true anophthalmos and an extreme degree of microphthalmos, for the matter could be determined only by microscopic examination of serial sections of the orbital contents. This would be of small clinical importance, even though the theoretic aspects are interesting.

ETIOLOGY

May [2] stated that congenital anomalies of the eyeball are rare and may be bilateral. In anophthalmos the eyeball is replaced by a small solid or cystic mass. Parsons [3] stated the belief that even though the eyeball may apparently be absent (congenital anophthalmos) there are always microscopic vestiges of ocular tissues. In Berens' textbook,[4] congenital abnormalities are classified as (1) those due to errors of development, which may occur at any stage in fetal life, e. g., anophthalmos, microphthalmos and coloboma of the uveal tract, and (2) those due to intrauterine inflammation. The role of intrauterine inflamma-

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1. Mann, I.: Developmental Abnormalities of the Eye, Brit. J. Ophth. **65**: 72, 1937.

2. May, C. H.: Manual of the Diseases of the Eye, Baltimore, William Wood & Company, 1941.

3. Parsons, J. H.: Diseases of the Eye, New York, The Macmillan Company, 1942.

4. Berens, C.: The Eye and Its Diseases, Philadelphia, W. B. Saunders Company, 1938.

tion has been denied; however, apart from other evidence, the microscopic appearance in such conditions as congenital anterior staphyloma and macular coloboma so closely resembles that found as a result of inflammatory lesions during extrauterine life that it is reasonable to assume a similar cause.[5]

Atkinson [6] reported congenital absence of the lacrimal gland in conjunction with anophthalmos; however, such a defect is an ophthalmologic curiosity and is seldom encountered, though its occurrence has been verified by postmortem examination. While some authors claim the existence of anophthalmos as an entity, others believe it to be only a more pronounced degree of microphthalmos. However, it has been noticed that the anomaly known as anophthalmos is usually bilateral and that microphthalmos is nearly always unilateral. Both conditions are believed to be the result of a failure of closure of the optic vesicle.

In cases of microphthalmos a cyst of the lower eyelid which contains a rudimentary eye is nearly always found. In almost all cases other congenital stigmas are seen, of which a miniature orbit is the commonest. Other defects, in the order in which they occur, are harelip, cleft palate, nasal cleft, supernumerary auricle and supernumerary digits. Some observers claim that associated deformities are less frequent in cases of microphthalmos than in cases of anophthalmos.

Microphthalmos has been described as a uniocular congenital deformity in which lack of development of one eye is in striking contrast to the development of the other. In some cases it may be said that the eye is not present at all, though a firm cystic tumor occupying the normal site of the eye in the orbit has sometimes been mistaken for an eye. Fuchs [7] described such a cyst as being attached to the lower lid, where it is seen glimmering with a bluish luster. When opened, the cyst is seen to contain a rudimentary retina, floating in a serous fluid. In cases of less marked deformity, coloboma, or congenital fissure of the iris and of the optic nerve, is usually present.

INCIDENCE

Anophthalmos occurs in man as a rare abnormality. In the literature, Collins [8] found only 30 cases of bilateral and 12 of unilateral anophthalmos, most of which were doubtful, as microscopic examination

5. Parsons, J. H.: The Pathology of the Eye, New York, G. P. Putnam's Sons, 1906.

6. Atkinson, D. T.: External Diseases of the Eye, ed. 2, Philadelphia, Lea & Febiger, 1937.

7. Fuchs, E.: Textbook of Ophthalmology, translated by A. Duane, Philadelphia, J. B. Lippincott Company, 1924.

8. Collins, E. T.: On Anophthalmos, Ophth. Hosp. Rep. **40**:429, 1886-1887.

was not made. Von Hippel [9] stated that the recorded number of cases of bilateral anophthalmos was 64 and that of unilateral anophthalmos 23, in 15 of which there were congenital anomalies. Sex incidence was not significant, and heredity was a rare factor. Collins [8] and Gallemaerts [10] noted that in the rare familial and hereditary cases the condition was obviously germinal in origin and in several of these it was unilateral. Other abnormalities were not present in most cases.

CORRECTION

A search of the literature showed no previous reports on attempts at esthetic correction of anophthalmos. In previous cases of loss of an eye in infants and children one of us (P. J. M.) had restored the defect by ophthalmoprosthesis, using the technic evolved while on duty at the United States Naval Dental School, the National Naval Medical Center, Bethesda, Md.[11] A number of naval personnel presented loss of an eye, the result of violent trauma, with destruction of areas of the lids and with redundant tissue in the cul-de-sac, so extensive that it was difficult to obtain retention of any type of prosthesis. These patients had received their injuries weeks, and even months, previously but had been unable to have the prosthesis made because of body wounds. Experience gained in obtaining an impression of the existing cul-de-sac, increasing its size by having the patient wear a prosthesis and then polymerizing ("curing") a larger prosthesis to replace the first was of great value in approaching the problem of minature cul-de-sacs found in anophthalmos.

A girl aged 7 months (fig. 1 *A* and *B*), after a thorough physical examination, was referred to the department of ophthalmology. A careful clinical examination did not disclose any evidence of remnants of the eye and, in the absence of microscopic biopsy, it may be assumed that a true anophthalmos existed. The cul-de-sac was so small that it was necessary to use a 20 cc. hypodermic syringe for injecting the impression material into the orbital socket. The first working cast shown in figure 2 indicates the miniature size of the cul-de-sac. From the cast a wax pattern was made; and after it was tried in the orbital socket, it was invested and "cured" into scleral material, as described in previous articles.[11]

This "cured" sclera was then polished and placed in the orbital socket. It was necessary to tape the eyelids in order to maintain the prosthesis within the socket, as the muscles of the lid had little tone and were poorly developed physiologically.

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9. von Hippel, E.: Anatomische Untersuchungen über angeborene Korektopie, Arch. f. Ophth. **51**:132, 1900.

10. Gallemaerts: Anophthalmia congenitale et familiale, Ann. d'ocul. **40**:490, 1924.

11. Murphy, P. J., and Schlossberg, L.: Eye Replacement by Acrylic Maxillofacial Prothesis, U. S. Nav. M. Bull. **43**:1085, 1944; Mil. Surgeon **96**:469, 1945. Murphy, P. J.; Pitton, R. D.; Schlossberg, L., and Harris, L. W.: Development of Acrylic Eye Prosthesis at the National Naval Medical Center, J. Am. Dent. A. **32**:1227, 1945.

Within a week the prosthesis was retained within the orbital socket without taping, and the patient was seen at regular weekly and biweekly intervals, as in orthodontic therapy. At these times the prosthesis was removed and the orbital socket thoroughly irrigated with isotonic sodium chloride solution, and the prosthesis was polished with prepared chalk and soft rag buffing wheels. Then, either it was reinserted or wax was added to the areas where growth seemed

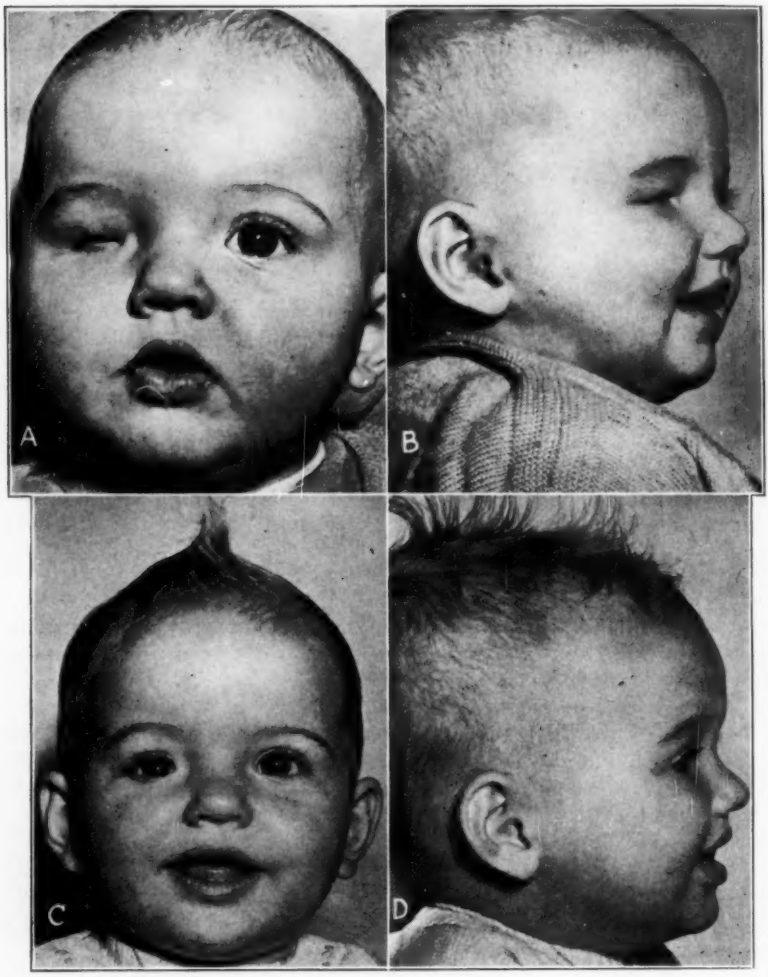
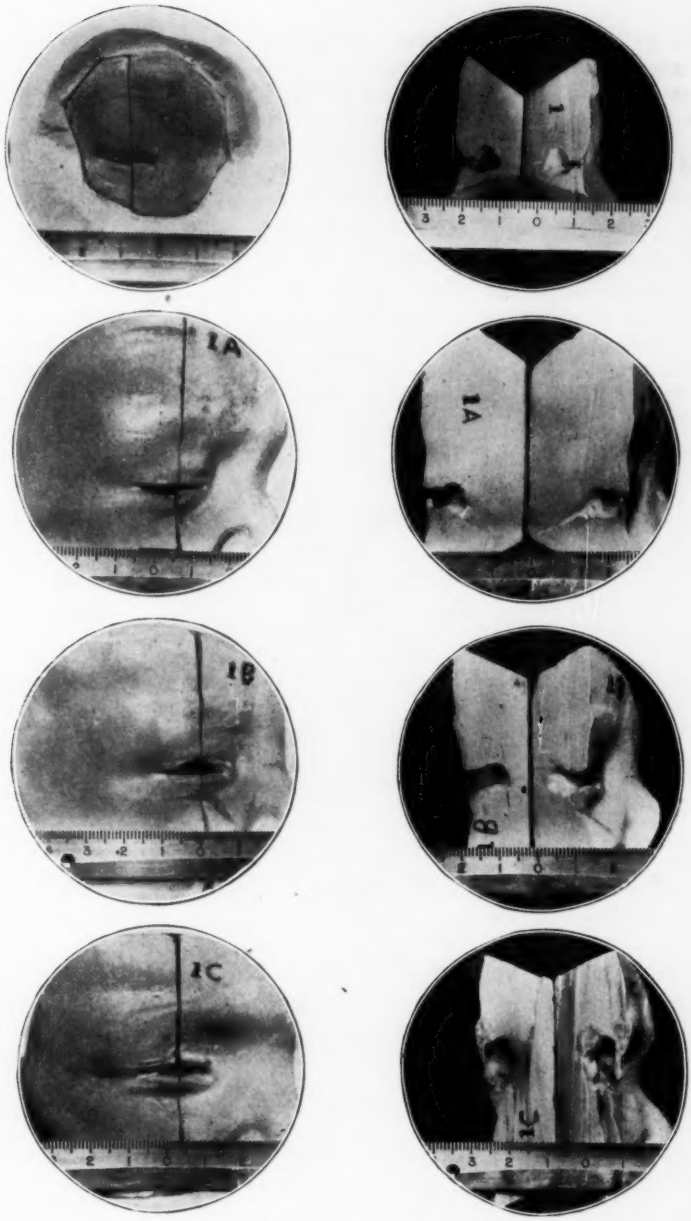


Fig. 1.—*A* and *B*, infant girl aged 7 months. *A*, collapsed upper lid and miniature cul-de-sac; *B*, profile showing failure in growth of orbital area, which would not develop further without physiologic function. *C* and *D*, infant after twelve months of treatment, showing growth of the upper lid and orbital fissure; *D*, a profile, shows filling out of the orbital area with normal curvature of the lid cilia.

to have occurred within the socket. This prosthesis was worn for several days with the wax attached, after which it was removed and reinvested in a flask, and clear acrylic was added to replace the waxed areas. The prosthesis was then polished and reinserted and worn again for a week, or for a longer period.



Fif 2.—Series of working casts. (*1*) Cast made Jan. 18, 1946: cul-de-sac approximately 9 mm. wide, 6 mm. deep and 5 mm. in vertical diameters; (*1A*) cast made May 17, 1946: cul-de-sac approximately 12 mm. wide, 10 mm. deep and 8 mm. in vertical diameter; (*1B*) cast made Sept. 13, 1946: cul-de-sac, approximately 15 mm. wide, 11 mm. deep and 10 mm. in vertical diameter; (*1C*) cast made Jan. 25, 1947: cul-de-sac approximately 19 mm. wide, 12 mm. deep and 16 mm. in vertical diameter.

It soon became evident that new working casts were necessary in order to keep pace with growth changes within the cul-de-sac. These were made at regular intervals, as shown in figure 2, and new wax patterns were made from them, to be "cured" in scleral acrylic and then worn as before. Figure 3 shows four of these prostheses, with the changes in growth and shape apparent.

At the end of twelve months of treatment, as shown in figure 1 *C* and *D*, the greater lid and the orbital fissure had approached the normal. In the profile of the face, a filling out of the orbital area, with normal curvature of the cilia of the lid, is definitely perceptible.

The psychologic effect observed during the period of growth stimulus of the orbital area and after the prosthetic restoration of the eye was very noticeable in this child. Even allowing for the prejudice of the parents, there was a definite improvement. The parents and relatives living with her were enthusiastic over the betterment in her social relations with other children during play periods. For example, the parents reported that before treatment was begun the neighborhood children referred to her as "that one-eyed baby." After sufficient space in

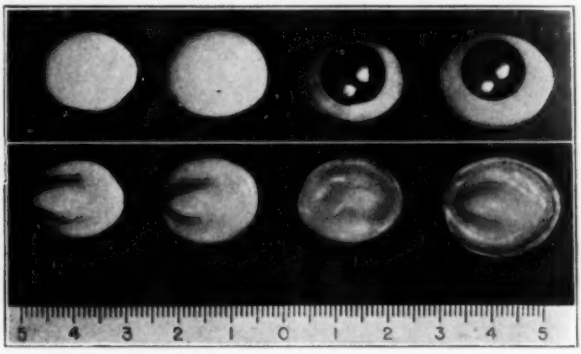


Fig. 3.—Upper figure: Four prostheses were inserted at intervals until the size of the sclera allowed for inlay of an iris. Lower figure: Growth of the cul-de-sac is apparent from this view of the posterior surfaces of the prostheses.

the cul-de-sac had been obtained to insert an iris in the prothesis, the children only occasionally used this designation in referring to her. The parents moved into another neighborhood and in this new environment she was accepted without reference to her ocular anomaly. The child seemed to realize her acceptance there with other children, and the parents reported that they observed a marked change in her feeling about herself (fig. 4).

Because the method of therapy was of an original nature and because of the encouraging results with this child, 5 other patients with anophthalmos were treated in a similar manner. The cases of 3 of these patients are reported.

A boy aged 9 months presented a clinically evident anophthalmos similar to that in the first case. *A* and *B* of figure 5 show this child after eight months of treatment, without the prosthesis in position. When treatment was begun, the patient had severe photophobia, and it was impossible to obtain adequate photographs. *C* and *D* of figure 5 show the child's appearance with the prosthesis in position.

These patients wear the prosthesis day and night and do not seem to be inconvenienced in any way. Tears flow over the face of the prosthesis, and because the posterior wall is in contact with the posterior wall of the cul-de-sac, any secretions accumulate in the inner and outer canthi of the palpebral fissure in a normal manner.

An infant or child with true anophthalmos presents the possibility of failure of facial growth without the ocular organ in position and without the opportunity for normal palpebral and ocular function.

Fig. 4.—The patient expresses her personal feeling of self assurance.

In figure 6 *A* and *B* is shown a woman aged 24 with a miniature cul-de-sac, infantile orbital features and anophthalmos clinically evident. This patient was treated in the same manner, with very evident changes in the cul-de-sac, as shown in figure 7 *A*, taken after nine months of treatment. Figure 7 *B* shows the changes in size of the prostheses that were worn, the first one being so small that it was necessary to use wax alone to obtain retention within the cul-de-sac. The patient was unusually enthusiastic about the results and gave cooperative home care between the intervals of treatment. The results shown in figure 6 *C* and *D* are notable, considering the period of time elapsed and the age of the patient.

Because it is reasonable to assume that, in still older patients, age might prevent the growth of the cul-de-sac, such a patient is shown in figure 8 *A* and *B*. This woman, who was past 40, had a miniature cul-de-sac and infantile features of the orbital area of the face. She

Fig. 5.—Infant boy aged 9 months at the time he was presented with a condition similar to that in the first case. (*A*) The prosthesis has been removed to illustrate the size of the palpebral fissure; (*B*) the profile shows necessity for maintaining the prosthesis in situ to preserve normal facial contour; (*C*) with the prosthesis in position the result of eight months of treatment is apparent, with the cul-de-sac approximately normal size; (*D*) profile with prosthesis in position shows restoration of the normal facial contours and stimulation of growth of the orbital area.

had never been able to wear a prosthesis of any type because the cul-de-sac was shallow and very small. A series of three prostheses

Fig. 6.—(*A*) A woman, aged 24, presented with a miniature cul-de-sac and failure in growth of the orbital area because of lack of correction. (*B*) Profile shows collapse of the lid cilia and depression in the orbital area of the facial contour. (*C*) Photograph nine months of treatment shows degree of restoration of the orbital area and increase in size of the palpebral fissure. (*D*) Profile shows increase in curvature of the lid cilia and degree of restoration to normal facial contour.

were made. The increased size of the cul-de-sac at the end of twelve months is shown in figure 8 *C* and *D*. The ptosis of the greater lid was overcome and the orbital area restored to more normal facial contours. It is hoped further to develop the orbital area by continued stimulation.

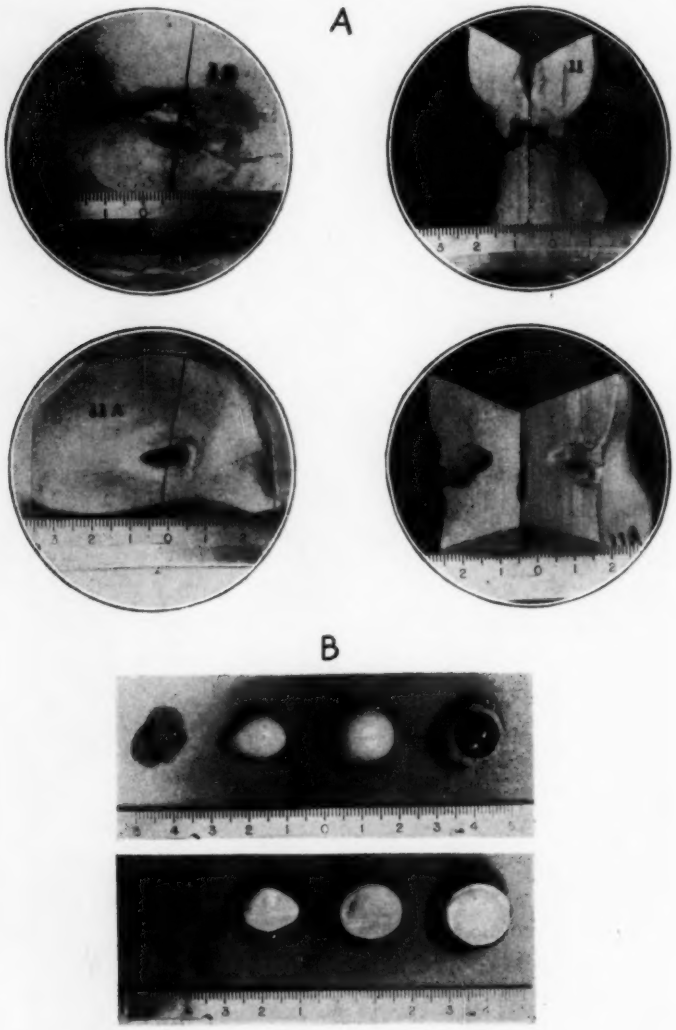


Fig. 7.—*A*: Upper circles: Cast made July 22, 1946: cul-de-sac approximately 8 mm. wide, 4 mm. deep and 6 mm. in vertical diameter. Lower circles: cast made April 14, 1947: cul-de-sac approximately 16 mm. wide, 15 mm. deep and 13 mm. in vertical diameter.

B: Upper figure: First prosthesis inserted was made of wax; then larger prostheses of scleral material were made until the iris could be inlayed into the sclera. Lower figure: Posterior views of the same prostheses show changes in the shape and size of the posterior wall of the cul-de-sac.

Fig. 8.—(*A*) Orbital area was infantile in development, due to lack of function since birth. (*B*) Profile view shows ptosis of the upper lid and marked endophthalmos. (*C*) The enophthalmos has been overcome considerably, and ptosis of the greater lid is improved. (*D*) Twelve months after treatment this prosthesis restores the orbital area to the extent shown.

SUMMARY

The literature has not previously been concerned with esthetic correction of unilateral anophthalmos but, rather, has discussed the etiology.

The distinction between true anophthalmos and microphthalmos is of small clinical importance so long as the cul-de-sac presents no pathologic condition before construction of the prosthesis is begun.

Even though the report of previous cases of anophthalmos is rare, the presentation of this technic as a method of correction will result in many more cases being made available for correction.

The technic previously developed for loss of eyes due to war injuries is ideal for an approach to the problem of the miniature cul-de-sac associated with anophthalmos.

From the results obtained in the esthetic correction of anophthalmos by the ophthalmoprosthetic technic in the cases reported, it is evident that growth of the cul-de-sac and the orbital area of the face may be stimulated, in a manner similar to the growth of muscle and bone associated with facial changes produced by orthodontic correction.

Infants and children do not seem to experience any pain or discomfort during the period of construction and wear the prosthesis without being aware of its presence in the orbital socket.

Redundant tissue within the cul-de-sac is absorbed under the prosthesis; the muscular tone improves, and the conjunctiva and underlying tissues become smooth and a healthy pink while the patient is wearing the prosthesis. This occurs because the prosthesis fits all the tissues snugly and does not permit the accumulation of secretions behind it.

Unless an attempt at esthetic correction is made in infancy or early childhood, it is reasonable to assume that the orbital area of the face and the cul-de-sac will not develop in pace with the other facial features, a condition observed in the adults whose cases are reported in this paper. The psychologic effect observed during the period of growth stimulation of the orbital area and after the adequate prosthetic restoration of the eye is very noticeable, even in very young children. In figure 4, the expression on the child's face may be interpreted as one of increased self assurance. Parents and relatives living with such children after esthetic correction has been completed are enthusiastic and state that they observe a notable improvement in the child's social relations within the home and with other children during play periods and at school.

The present need for continued research in the field of ophthalmoprosthesis and for further effort toward the esthetic correction of anophthalmos is of prime importance.

Fairmount at Welborn (4).

NONPERFORATING THERMOMETRIC CYCLODIATHERMY IN TREATMENT OF HYPERTENSIVE UVEITIS

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AND
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IN 1942 we recommended the use of nonperforating cyclodiathermy in treatment of various forms of intraocular hypertension. Since then, we have endeavored to improve this operation and to determine its indications and the mechanism of its hypotensive effect.[1]

During this period, while all scientific exchanges between the United States and Belgium were cut off, Albaugh and Dunphy [2] described a similar operation. This, however, differs from ours in several points, which we shall comment on later.

NONPERFORATING THERMOMETRIC CYCLODIATHERMY

Diathermy Apparatus.—A diathermy electrode is applied to the eyeball at the posterior edge of the ciliary body, and the heating of the tissues (fig. 1) is effected with the high frequency current.

The apparatus has two circuits: One, the diathermy circuit, generates the high frequency current and produces the heating of the tissues; the other, the thermometer circuit, provides for the measurement of the tissue temperature.

It is not necessary to describe the diathermy circuit, as it has no special features. We use a bipolar current. The passive electrode is placed on the patient's back. The active electrode, placed on the eyeball, is made of a copper cylinder, 0.6 or 0.8 by 1 mm.

The thermometer circuit is made according to Coppez' [3] diagram (fig. 2). It includes a cold thermoelectric couple, immersed in ice, and a hot thermoelectric couple, placed on the eyeball at the same place as the active diathermy electrode. The manufacture of small thermoelectric couples presents difficulties. We shall briefly describe the hot couple.

It is made of two wires—one of copper, the other of constantan. The diameter of the copper wire is 0.6 or 0.8 mm. This is the active electrode described in the

From the Ophthalmologic Clinic, University of Liége, Hospital of Bavière.

1. Weekers, L., and Weekers, R.: Ophthalmologica **104**:1, 1942; **109**:218, 1945; Acta ophth. **24**:1, 1946; Ann. d'ocul. **180**:10, 1947; Bull. Soc. belge d'opht. **81**:50, 1945; **85**:38, 1946.

2. Albaugh, C. H., and Dunphy, E. B.: Cyclodiathermy: Operation for Treatment of Glaucoma, Arch. Ophth. **27**:543 (March) 1942.

3. Coppez, L.: (*a*) Ophthalmologica **109**:80, 1945; (*b*) Bull. et mém. Soc. franç. d'opht. **59**:237, 1946.

diathermy circuit. It therefore belongs both to the thermometer and to the diathermy circuit. The diameter of the constantan wire is 0.1 mm. It belongs to the thermometer circuit only. These two wires are welded to form the thermoelectric couple. This welding was carried out in two ways, and both were satis-

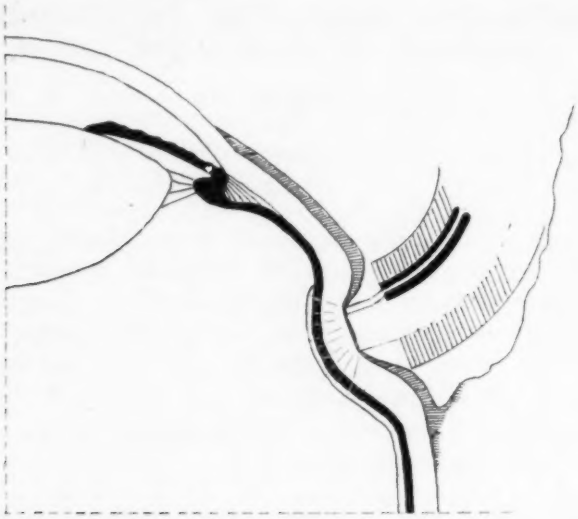

Fig. 1.—Scheme showing the place of application of the thermometric electrode, on the posterior edge of the ciliary body, 8 mm. from the limbus.

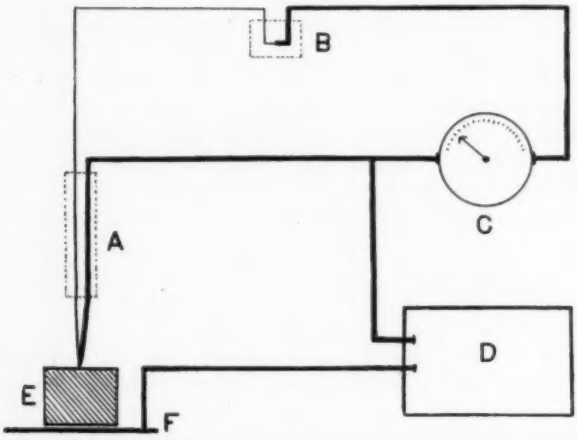

Fig. 2.—Scheme of the diathermic and thermometric circuits (from Coppez [3b]). *A* indicates hot thermoelectric couple (active electrode); *B*, cold thermoelectric couple (immersed in ice); *C*, millivoltmeter, used as a thermometer; *D*, diathermy apparatus; *E*, patient; *F*, passive electrode.

factory (fig. 3). When the two couples of the thermoelectric circuit have different temperatures, there is a difference of potential between them. The latter is proportional to the difference of temperature. It is measured by the millivoltmeter placed

in the circuit. The latter is graduated empirically in degrees centigrade and serves as a thermometer.

Technic of the Operation.—The anesthesia of the eyeball is obtained by instillations of cocaine and epinephrine and by a retrobulbar injection of 2 cc. of 4 per cent

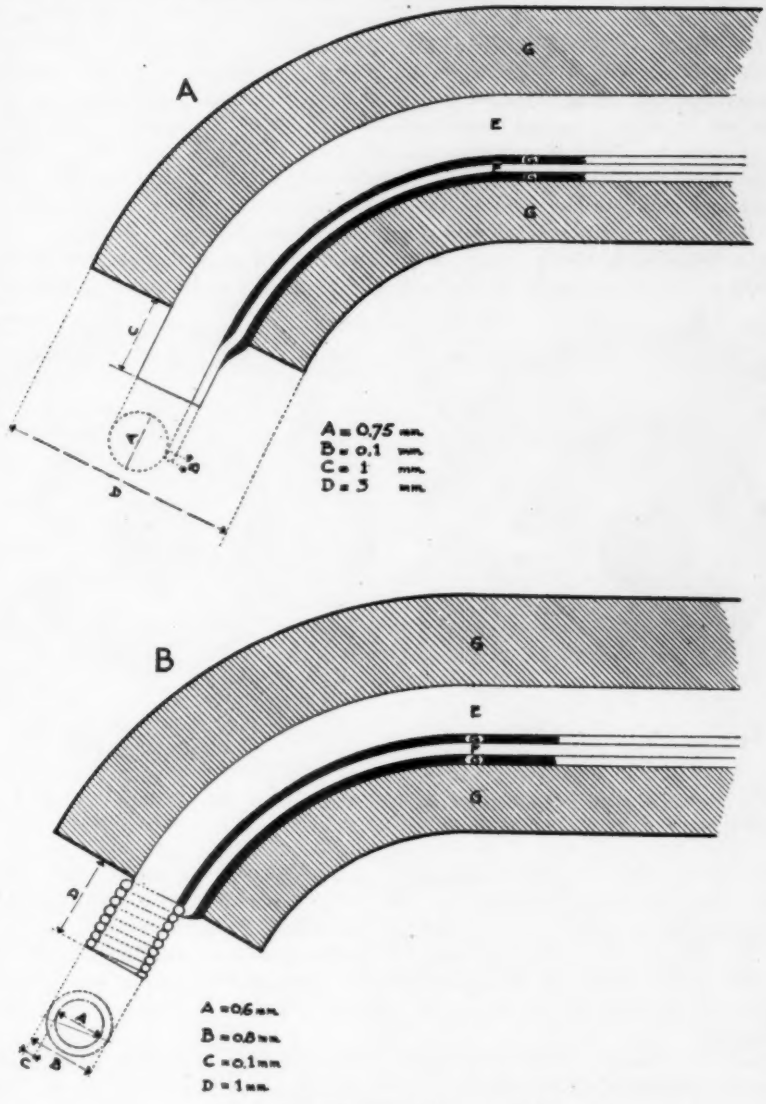

Fig. 3.—Thermometric electrodes.

In both diagrams, *E* indicates the copper wire; *F*, the constantan wire, and *G*, the insulation.

procaine hydrochloride. If sufficient time elapses (ten minutes at least), this anesthesia renders the operation painless.

The lids are held open with a blepharostat. The electrode is placed directly on the eyeball, without dissection of the conjunctiva. The use of forceps is not necessary. The pressure of the electrode fixes the eyeball.

The place where the electrode is applied should be carefully chosen. The effects on tension and the risk of complications are greater the nearer this site is to the limbus. The electrode must be placed, at the ora serrata, at the back of the ciliary body, 8 mm. from the limbus (fig. 1). The number of applications varies from twelve to twenty (fig. 4). Twelve to sixteen applications are, as a rule, sufficient to normalize the ocular pressure permanently in cases of hypertensive uveitis. When the electrode is applied twelve times, the coagulated areas in the conjunctiva are separated by a band of apparently normal tissue. When the electrode is applied twenty times, the coagulated areas touch one another. It is the same with the areas of postoperative chorioretinitis, as shown by the ophthalmoscope; these will be described later. Each application lasts fifteen seconds.

The temperature shown by the millivoltmeter used as a thermometer at the moment of the application of the electrode is that of the conjunctiva, i. e., approxi-

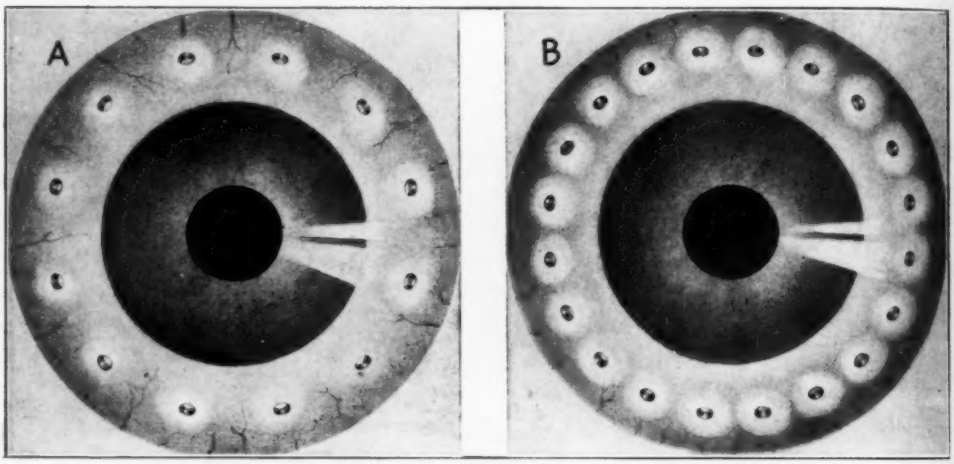

Fig. 4.—Diathermic coagulation made 8 mm. from the limbus. *A*, twelve coagulations; *B*, twenty coagulations.

mately 30 C. The rheostat is adjusted in such a way that the temperature rises rapidly when the current is turned on. We try to reach 90 C. at the fifth second. This temperature must be maintained as constant as possible for ten seconds (fig. 5). At the fifteenth second, the current is turned off and the electrode is removed. It is necessary, in order to avoid desiccation of the cornea and to prevent a lesion, to close the eyelids for a few moments after three or four consecutive applications.

After the operation, penicillin ointment and a dressing are applied three times a day for forty-eight hours. After that, it is sufficient to wash the eye two or three times a day with a solution of tepid isotonic sodium chloride solution U. S. P. as long as the postoperative reaction lasts, that is, for two or three weeks. In case of hypertensive uveitis, we carry on the treatment with atropine when necessary.

Observations.—After the operation, when the pupil is wide, the chorioretinal lesions caused by the diathermy burn can be observed with

the ophthalmoscope. For six to seven days, the ophthalmoscopic image consists of a ring of retinal edema. Each patch of edema is circular, slightly raised, 3 or 4 papillary diameters in width and close to the next patch. The edema is white, with a few hemorrhages; the retinal vessels are bent when passing from the normal to the edematous retina (fig. 6*A*). Ten days after the operation, the edema is less, and the patches are smaller and less prominent. Brownish, irregularly distributed pigmentary spots appear in the retina, and the hemorrhages are less visible (fig. 6*B*).

Twenty to thirty days after the operation, the patches have a new aspect and the chorioretinal scars are now formed; they are flat, circular, with sharp edges; the diameter is less than 3 papillary diameters, and the retina and choroid are atrophic. A few vessels of the retina and choroid remain, clearly visible against the white background of the

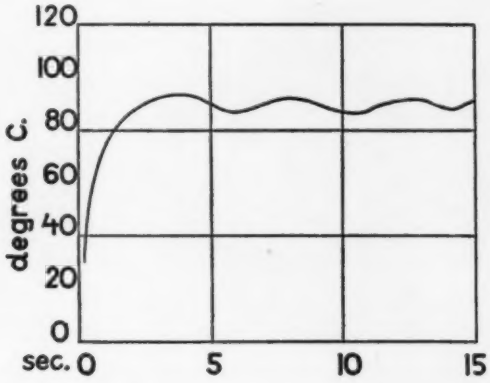

Fig. 5.—Increase in the tissue temperature produced by the diathermic current.

sclera. There are dense pigmented spots, with irregular edges. The chorioretinal patches along the ora serrata are somewhat similar to the postoperative scars after retinal dialysis (fig. 6*C*).

The successive improvements in the technic of nonperforating cyclodiathermy have made it an easy and well controlled operation, the effects of which can be graduated at will. When correctly performed, it is quite without danger. Its hypotensive effect is considerable and lasts according to the degree of the intraocular hypertension. Its indications have become precise. In addition to the hypertensive uveitis studied in this paper, nonperforating cyclodiathermy should also be used in treatment of (*a*) hypertension persisting after a filtering operation; (*b*) absolute glaucoma, especially when the eyes are painful, and (*c*) intraocular hypertension following corneal transplantation.

The operation described by Albaugh and Dunphy [2] presents features which are similar to ours, namely, the use of a nonperforating, flat

electrode, and the application of this electrode to the posterior extremity of the ciliary body. It differs from our operation, however, in three points. 1. Albaugh and Dunphy perform a dissection of the conjunctiva, which we do not regard as necessary. 2. They operate on one-half the circumference of the ciliary body. Previous experimental researches have demonstrated that when the operation is performed in a small territory it becomes necessary to use a more intense diathermy current to obtain a sufficient effect on the ocular pressure (Weekers and Weekers [1]). 3. They do not use a thermometer electrode, which enables us to regulate our intervention and to repeat it under identical conditions.

Thermometric nonperforating cyclodiathermy, carried out in the way we have described, does not lead to postoperative complications. From this point of view, it is quite different from Vogt's perforating

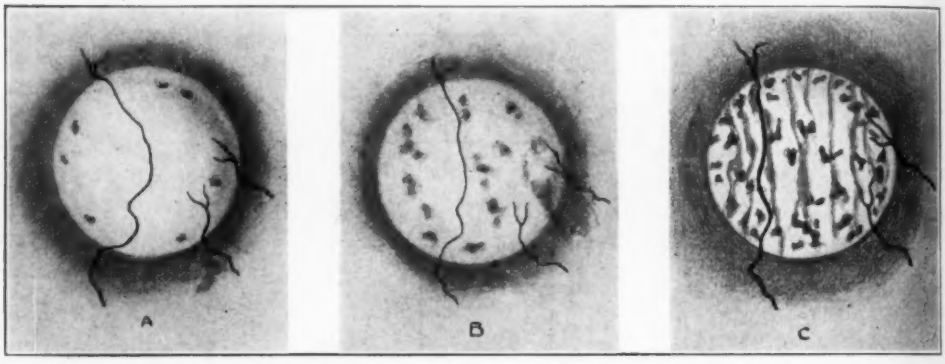

Fig. 6.—Ophthalmoscopic images of the diathermic coagulation at the ora serrata. *A* (twenty-four hours after operation): white, salient edema 4 papillary diameters wide; a few small blood suffusions. *B* (ten days after operation): The edema allows the retinal pigment to show through. *C* (thirty days after operation): Atrophy of the retina and choroid and persistence of the vessels; irregular distribution of the retina and choroid pigments. The sclera is visible.

cyclodiathermy (*Diathermiestichelung*), the complications of which are known (corneal ulcer, iritis, cataract and sympathetic ophthalmitis). Sugar [4] observed that Vogt's cyclodiathermy leads to synechias in the iridocorneal angle. Gonioscopic observations, now in progress, demonstrate that such is not the case after nonperforating thermometric cyclodiathermy. In the case of iritis, this operation does not even stimulate the formation of preexisting synechias in the angle of the iris.

Results of Treatment of Hypertensive Uveitis with Nonperforating Thermometric Cyclodiathermy.—Treatment of ocular hypertension complicating various forms of iridocyclitis and uveitis is a difficult problem.

4. Sugar, H. S.: Gonioscopy and Glaucoma, Arch. Ophth. **25**:674 (April) 1941.

Miotics (pilocarpine, physostigmine and dis-isopropyl fluorophosphate [DFP]) are contraindicated; they increase the ocular congestion, facilitate the appearance of synechias and jeopardize the future of the eye and its functions.

Mydriatics, on the other hand, have a favorable influence on the uveitis and, consequently, on the intraocular hypertension. The instillation of drops of atropine (1 per cent) in an eye with hypertensive uveitis is without danger. We often use it, and the results are most favorable. The instillation of drops of epinephrine hydrochloride, 2 per cent, is useful to break down recent synechias in cases of the acute form (Weekers, Joiris and Bonhomme [5]).

When the mydriatic treatment is insufficient to decrease the tension, we practice a retrobulbar injection of alcohol (1.5 cc. of 40 per cent alcohol); this reduces the ocular pressure and has a favorable action on the iridocyclitis (Weekers,[6] Magitot and Morax [7]).

An eye with iridocyclitis can often bear a moderate increase of tension for a long period without any visual decrease.[8] Later, temporizing becomes dangerous, and the operation can no longer be postponed. In such cases, we used to practice iridencleisis ab externo, as described by L. Weekers in 1936.[9] The results were satisfactory. They have recently been confirmed by Kalt.[10] This author operated in 22 cases of hypertensive iridocyclitis. The ocular tension was definitely normalized in 86 per cent and the visual acuity was improved in 60 per cent of the cases.

We now prefer nonperforating cyclodiathermy in the treatment of hypertensive uveitis. This new operation has been performed on 12 patients with uveitis complicated by ocular hypertension, including 10 patients with uveitis of tuberculous origin, 1 patient with diabetic uveitis and 1 patient with Besnier-Boeck-Schaumann disease (generalized sarcoidosis).[11] In other words, all the patients had chronic, malignant types of uveitis, complicated by a definite and dangerous rise in ocular pressure.

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5. Weekers, L.; Joiris, P., and Bonhomme, F.: Arch. d'opht. **3**:97, 1939.

6. Weekers, L.: Ann. d'ocul. **176**:81, 1939.

7. Magitot, A., and Morax, P.: Bull. Soc. d'opht. de Paris **49**:617, 1937.

8. The visual functions must be tested with the most sensitive methods: angioscotometry; campimetry in weakened light; perimetry with luminous spots of low brilliance, and measurement of fusion frequency and of dark adaptation.

9. Weekers, L.: Arch. d'opht. **53**:166, 1936.

10. Kalt, M.: Bull. et mém. Soc. franç. d'opht. **59**:230, 1946.

11. Recently, we have treated several more patients, among whom were one with Fuchs's heterochromia and one with syphilitic uveitis, both complicated by hypertension. The immediate results were favorable, and the patients are being kept under observation for further study.

The results are presented diagrammatically (fig. 7). The initial tensions, before the cyclodiathermy, vary from 30 to 50 mm. of mercury. The intervention in most cases produces a rapid and considerable fall of the ocular pressure. Fifteen days after the cyclodiathermy, the ocular pressure is in the majority of cases lower than 23 mm. of mercury. The hypotensive effect of cyclodiathermy lasts a long time and is generally sufficient to neutralize the phase of hypertension due to the uveitis. In 1 case (Besnier-Boeck-Schaumann disease) a relapse of the uveitis, complicated by further hypertension, compelled us to repeat the operation three months later. This was followed by an immediate and lasting fall in tension. These results are satisfactory, considering the serious nature of the uveitis and the usual

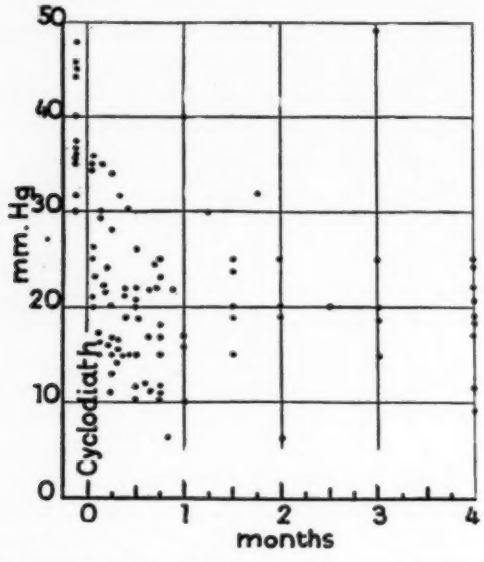

Fig. 7.—Hypotensive effects of thermometric nonperforating cyclodiathermy in 12 cases of hypertensive uveitis.

malignancy of the resulting hypertension. We now apply cyclodiathermy very early, without even carrying out the preliminary retrobulbar injection of alcohol.

When there is pupillary seclusion, cyclodiathermy is contraindicated. It is necessary in such cases to reestablish the passage of the aqueous humor through the diaphragm of the iris. Iridencleisis is indicated in these cases. The only object of cyclodiathermy is to relieve ocular hypertension; the local treatment with mydriatics and the general treatment should not be interrupted.

It is difficult to judge the influence of cyclodiathermy on the inflammatory process. The anatomic changes are often serious at the time

of intervention (synechias, cloudiness of ocular media, cataract). Sometimes one has the impression that, apart from its hypotensive effect, cyclodiathermy influences favorably the inflammatory process of the uveitis. One thing is certain: It removes the immediate and serious threat of hypertension.

CONCLUSIONS

Thermometric nonperforating cyclodiathermy should be used in treatment in certain cases of ocular hypertension. Its main advantages are as follows: (*a*) It is easy to perform; (*b*) opening of the sclera is avoided; (*c*) the operation can be regulated at will; (*d*) it does not lead to any complications.

The hypotensive effect of nonperforating diathermy is definite and lasting in accordance with the nature of the glaucomatous process. It is less than that of iridencleisis and is of shorter duration.

The main indications for thermometric nonperforating cyclodiathermy are as follows: (*a*) uveitis complicated by intraocular hypertension; (*b*) hypertension persisting after a filtering operation; (*c*) painful, absolute glaucoma, and (*d*) intraocular hypertension after corneal transplantation.

Hospital of Bavière.

LYMPHOSARCOMA OF THE EYELID

Report of Case, With Death in Forty Days

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LESS THAN 1 per cent of all lymphosarcomas originate in the region of the eye. When it does arise in the lid or the orbit, lymphosarcoma, although it infiltrates to a limited extent, tends to be a well circumscribed and slow-growing tumor; the other tissues of the body are not usually involved for many months or years. Lymphosarcoma also appears microscopically benign, with relatively well differentiated cells and few mitoses. Surgical removal may be followed by survival for many years, and irradiation has proved efficacious in ameliorating the disease for considerable periods. Cases of lymphosarcoma of the eyelid and/or orbit have recently been reported by Metivier,[1] Cookson and MacRae,[2] Michail,[3] Tooke,[4] Wheeler,[5] Jensen,[6] Siatto,[7] Hine,[8] Perera,[9] Black [10] and Rados.[11]

From the Institute of Ophthalmology of the Presbyterian Hospital in the City of New York.

1. Metivier, V. M.: Lymphosarcoma of Eyelid, Brit. J. Ophth. **21**:202-206, 1937.

2. Cookson, H. A., and MacRae, A.: Lymphoid Tumor of the Lacrymal Gland, Brit. J. Ophth. **22**:385-391, 1938.

3. Michail, D.: Sur les lymphomes symetriques des glandes lacrymale, Ann. d'ocul. **175**:565-581, 1938.

4. Tooke, F. T.: A Case of Aleukemic Lymphosis Involving the Upper Lids, with Pathologic Findings, Tr. Am. Ophth. Soc. **36**:268-276, 1938; Brit. J. Ophth. **23**:444-454, 1939.

5. Wheeler, M. C.: Malignant Neoplasm of the Eyelid: Report of Two Cases, Arch. Ophth. **20**:682 (Oct.) 1938.

6. Jensen, J. P.: Conjunctival Lymphoma, Acta ophth. **18**:67-75, 1940.

7. Siatto, G.: Contributo alla conoscenza del reticuloma della congiuntiva: Osservazione clinico-istologica, Rassegna ital. d'ottal. **9**:477-486, 1940.

8. Hine, M. L.: Report of a Case of Lymphoma of the Orbit, Brit. J. Ophth. **26**:297-301, 1942.

9. Perera, C. A.: Lymphosarcoma of the Lacrymal Gland: Report of a Case with Giant Lymph Follicle Hyperplasia, Arch. Ophth. **28**:522-529 (Sept.) 1942.

10. Black, G.: Reticulum Cell Sarcoma, Tr. Ophth. Soc. U. Kingdom **62**: 316-319, 1943.

11. Rados, A.: Reticulum Cell Sarcoma of the Conjunctiva, Arch. Ophth. **35**:400-414 (Jan.) 1946.

More commonly, lymphosarcoma begins in the cervical, axillary, mediastinal or mesenteric lymph nodes, or in the lymphoid tissue of the nasopharynx, stomach or intestine. It is generally a malignant tumor, expanding in a frankly invasive and destructive manner, sometimes like an ordinary neoplasm, with a focal origin and spread by infiltration and metastasis; but often it shows its relationship to the leukemias and to Hodgkin's disease by an apparently pluricentric origin, occurring simultaneously or successively. Secondary invasion usually involves other lymph nodes, both near and distant, to be followed by the infiltration of other organs containing lymphoid tissue, such as the liver, lungs and kidneys. Pathologically, the predominant cell may be any one of the lymphoid series, thus giving rise to the lymphocytic cell type, the reticulum cell type and the giant follicle cell lymphosarcoma. The cell type may change during the course of the disease, or different cell types may be found in different locations in the same patient. Clinically, in addition to the symptoms referable to the tumor, there may be anemia, due to depression of red blood cell formation, and a moderate leukocytosis is seen in about half the cases. Lymphosarcoma must be distinguished [12] from other metastatic tumors of the lymphatic system, such as lymphatic leukemia, Hodgkin's disease, chloroma, pseudoleukemia, mycosis fungoides, Mikulicz' syndrome and, most important of all, benign hyperplasia of lymphatic tissue. It is probable that many of these conditions are closely related and differ only in the character of the proliferative activity. In the majority of cases, the tumors in the region of the eye are probably part of a systemic disease that will sooner or later involve a great portion of the lymphoid tissue of the body.

The present case is reported, not because it represents a rare tumor, but for its unusual features. Clinically, the case was unusual in that (1) the lesion was considered an atypical, low grade inflammatory process by all who examined the patient, and (2) the disease progressed

12. The differentiation of these related conditions is one of the complex problems of pathology; for a discussion of this subject, attention is invited to the following publications: (*a*) Callender, G. R.: Tumors and Tumor-Like Conditions of the Lymphocyte, the Myelocyte, the Erythrocyte, and the Reticulum Cell, Am. J. Path. **10**:443-466, 1934. (*b*) Ewing, J.: Neoplastic Diseases, Philadelphia, W. B. Saunders Company, 1940, pp. 396-433. (*c*) Krumbhaar, E. B.: The Lymphomatoid Diseases: So-Called Lymphoblastomas, J. A. M. A. **106**: 286-291 (Jan. 25) 1936. (*d*) Kundrat, L.: Ueber Lympho-Sarkomatosis, Wien. klin. Wchnschr. **6**:211 and 234, 1893. (*e*) Minot, G., and Isaacs, R.: Lymphoblastoma and Malignant Lymphoma, J. A. M. A. **86**:1185-1189 (April 17) 1926. (*f*) Robb-Smith, A. H. T.: Reticulosis and Reticulo-Sarcoma: A Histological Classification, J. Path. & Bact. **47**:457-480, 1938. (*g*) Stout, A. P.: Human Cancer, Philadelphia, Lea & Febiger, 1932, pp. 795-838.

rapidly to a fatal termination in forty days. Pathologically, the neoplasm in this case is unique because of (1) the meager amount of involvement of the lymph nodes and (2) the rapid, destructive spread to involve all the viscera and other tissues of the body.

REPORT OF CASE

Mr. B. J. B., a Jewish machinist aged 49, consulted his family physician on May 9, 1947, with the complaint that a hot chip of metal had flown into his right eye two days previously. The piece of steel had been removed immediately in the shop, but the following day the eye was red, with a purulent discharge. His physician made a diagnosis of acute purulent conjunctivitis and prescribed sulfathiazole ophthalmic ointment. On May 14 there developed an inflammation of the right lower lid near the inner canthus, which subsided with treatment. Two weeks later the lids of the right eye began to swell. He went to see his physician again on June 2, and hospitalization for the administration of penicillin was advised. After two days of this regimen sulfadiazine was combined with the penicillin, and on June 9 they were both discontinued and streptomycin treatment was instituted. Two days later penicillin was given again, this time in combination with streptomycin.

An ophthalmologist was then asked to see the patient, and the diagnosis of orbital cellulitis and abscess of the right lower lid was made. Incision into the apparent abscess was performed but no discharge was obtained. Roentgenograms of the orbit and sinuses revealed no abnormality. Examination of the blood showed a white cell count of 15,450, with 78 per cent polymorphonuclear leukocytes, 19 per cent lymphocytes, 2 per cent monocytes and 1 per cent eosinophils. Cultures of material from the conjunctival sac yielded only diphtheroids and Staphylococcus albus. There was no pain or discomfort and no fever. On June 18 the antibiotics were discontinued because it was thought they were masking the picture. At this time the swelling of the lids had progressed so that the patient was unable to open his eye. In the last examination of the globe itself, on that date, the media and fundus appeared normal. The patient was then referred to the Institute of Ophthalmology of the Presbyterian Hospital, to the service of Dr. Algermon B. Reese, for further study.

The patient was admitted to the Institute of Ophthalmology on June 24; at this time he presented a hard, red swelling of the right eyelids and the right side of the face, including the submaxillary region. The right eye was not examined because the lids could not be everted or retracted. No lymphadenopathy was found, but there appeared to be an abscess in the submaxillary region. General physical examination disclosed nothing abnormal. The patient had never had any serious illness; he had had a submucous resection at the age of 12.

The impression at the time of admission was that of a fungous infection of the right orbit and the right side of the face. Figure 1 is a photograph of the patient at the time of admission to the Institute. On the day following admission, an incision was made in the medial half of the right lower lid and carried back into the orbit; the floor of the orbit was explored to the apex, but no pus or exudate was obtained. Cultures for bacteriologic examination were taken at various depths of the incision, but subsequent investigation of these cultures revealed only a few, nonpathogenic, bacteria. Cultures of tears and of material from the conjunctiva, lid margins and skin of the face disclosed nothing more than

the normal flora. Blood cultures were sterile. Roentgenograms of the heart and lungs were observed to be well within the limits of normal variation. Stereoscopic roentgenograms of the skull were reported to show some necrotic teeth, increased density of the soft tissue of the right orbit, massive swelling of the soft tissues of the right side of the face, clouding of the right ethmoid labyrinth, thickening of the lining membrane of the right antrum and clear sinuses on the left side. The blood count at this time was as follows: red cells, 4,120,000; hemoglobin, 90 per cent, or 13.1 Gm. per hundred cubic centimeters; white cells, 17,000, with 73 per cent polymorphonuclear leukocytes, 15 per cent lymphocytes, 4 per cent monocytes, 2 per cent eosinophils, 1 per cent basophils and 5 per cent band forms. All other laboratory procedures were noninformative.

Fig. 1.—Photograph of the patient at the time of his admission to the hospital.

During the first week in the hospital, the mass increased greatly in size, extending down over the angle of the jaw to involve the whole right side of the neck. The nose was displaced farther to the left, and the right ear was pressed posteriorly. It became difficult for the patient to open and close his jaws; there was no pain, but only mechanical discomfort. The right eyelids were solidly closed. The surgical incision in the right lower lid did not heal. The mass in the neck did not resemble typical cervical adenopathy but appeared to be a subcutaneous inflammatory swelling, continuous with that of the face. At this time, a few small nodes became palpable in the right axilla, and the liver was found to be 2 fingerbreadths below the costal margin. On June 30 a biopsy

was performed on the mass over the angle of the jaw; microscopic examination of the sections disclosed a highly malignant lymphosarcoma of the reticulum cell type.

In the second week of his hospitalization, the patient's general condition deteriorated rapidly; he became silent, morose and depressed. He ate little, and eating was followed by nausea and vomiting. His fluid intake and output decreased markedly. With evidence of widespread dissemination of the disease nitrogen mustard (tris-[2-chloroethyl] amine hydrochloride) therapy was favored initially, rather than irradiation. A course of nitrogen mustard (12 mg. daily) was given on July 4, 5 and 6. On the following day there was a striking decrease in the size of the tumor of the face and neck, and the cervical mass was scarcely palpable. The swelling was reduced to such an extent that the lids were easily opened and

Fig. 2.—Photograph of the patient one day after completion of the course of nitrogen mustard (one day before his death).

the eye could be examined; no pathologic process was found. Figure 2 is a photograph taken on July 7. The patient suffered increasing nausea and vomiting; infusions of dextrose solution were given. The blood count now showed 4,190,000 red cells, 78 per cent hemoglobin and 2,900 white cells, with 58 per cent polymorphonuclear leukocytes, 20 per cent lymphocytes, 8 per cent monocytes and 14 per cent band forms.

On the morning of July 8 the patient evidenced definite, acute cardiac distress; this was the first time that cardiac symptoms had been noted. The nurse found him too weak and unsteady to go to the bathroom; while using the bedpan, he shouted for help, and the nurse found him unconscious. A few moments later a member of the house staff pronounced him dead, evidently from respiratory arrest.

PATHOLOGIC EXAMINATION

Biopsy of Specimen from Jaw (June 30).—The biopsy specimen yielded sections showing skin and subcutaneous tissue on one aspect. Microscopically, the subcutaneous tissue was entirely replaced by a broad sheet of large, pale cells with ovoid or rounded nuclei, among which one could easily see many mitoses. The cells showed no tendency toward any grouping or structure; they were simply packed closely together. They contained moderate amounts of pale cytoplasm; there were granules of chromatin in the nuclei, lending a reticulated appearance. The uniformity of the cellular morphology was striking. No reticular network could be made out in these sections; the normal subcutaneous tissue was entirely

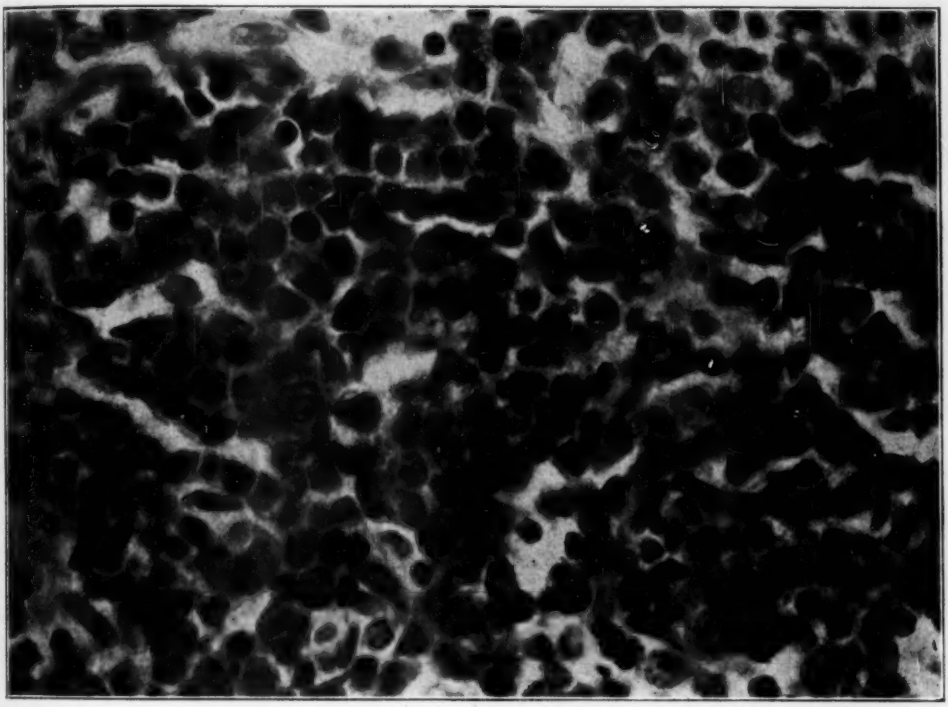

Fig. 3.—Photomicrograph of a section from the biopsy specimen from the jaw.

obliterated. The tumor cells were at least twice as large as a lymphocyte; therefore, this tumor was considered a reticulum cell type of lymphosarcoma. The histologic picture was similar to that of metastatic carcinoma in a lymph node but for the lack of any tendency to glandular or epithelial structure. Figure 3 is a photomicrograph from a section of the biopsy specimen.

Postmortem Examination.—Macroscopic Observations: The body was that of a well developed and well nourished white man of middle age. Externally, one saw the closed right eye and the tumor of the right side of the face and neck. Matted lymph nodes could be palpated in the right cervical and submaxillary areas; a few discrete nodes were present in the right axilla. Internally, the musculature

of the right ventricle of the heart exhibited a peculiar gray color; otherwise the thoracic cavity appeared normal. The liver could be palpated 2 fingerbreadths below the right costal margin; on section through the parenchyma, a small hemangioma, about 7 cm. in diameter, was disclosed. The external surface of the kidneys exhibited many light gray areas, from 1 to 2 cm. in diameter, which were not raised above the renal surface; on section, these gray lesions were seen to extend into the renal cortex. The intestine showed scattered, patchy, black lesions throughout the mucosal surface; there was no evidence of ulceration or bleeding into the lumen. The lymph nodes of the mesentery were enlarged and appeared yellow on cut surface.

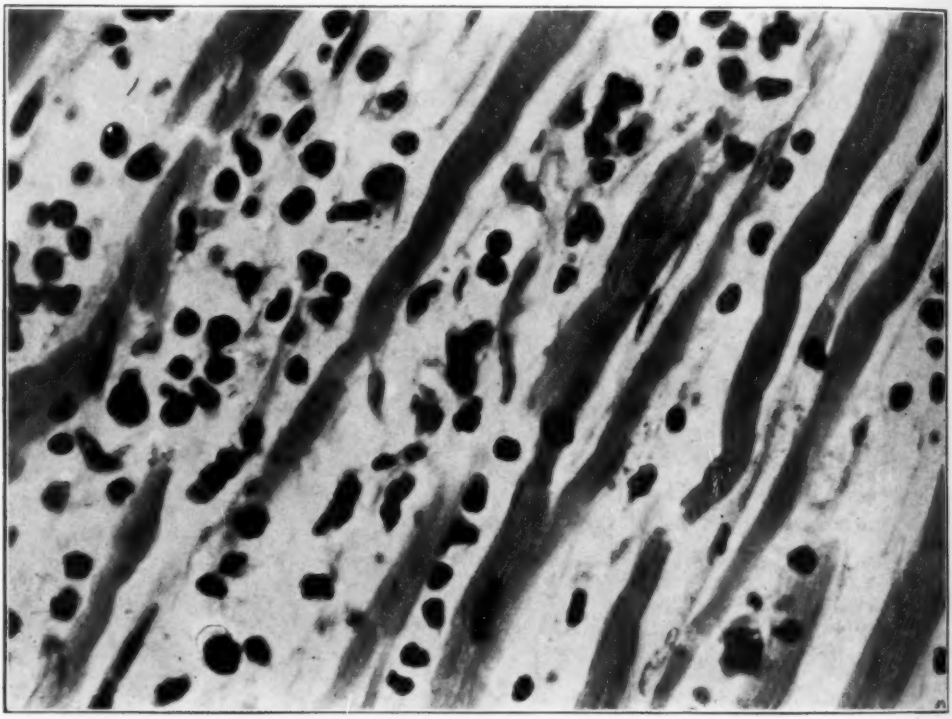

Fig. 4.—Photomicrograph of a section from the right ventricle, showing the wide separation of the cardiac muscle fibers by the tumor cells.

Microscopic Observations: Microscopically, extensive infiltration of the tumor cells was observed in the heart, liver, kidneys, spleen, stomach, pancreas and intestine.

Heart: The myocardium of the right ventricle showed an extensive, diffuse infiltration of hyperchromatic cells (closely resembling lymphocytes) with round nuclei and a slight amount of basophilic cytoplasm; again, the uniformity of these cells was striking. The muscle fibers, which appeared very thin and scanty, were widely separated by the accumulations of these cells. Figure 4 is a photomicrograph of a section from the right ventricle. It was amazing that the right ventricle was so largely replaced by tumor tissue and yet the patient showed no evidence

of cardiac failure until the day of his death. The left ventricle did not exhibit this extensive invasion; only small deposits of the tumor cells were seen under the epicardium. Moderate arteriosclerotic changes in the aorta and slight intimal thickening of the coronary vessels were the only other cardiac lesions noted.

Lungs: There were several small areas of infiltration of tumor cells about the arteries. The alveoli and most of the interstitial tissue showed no infiltration and appeared normal.

Liver: Localized groups of the same kind of tumor cells were present about the portal radicles. The section taken from the hemagioma showed endothelium-lined spaces containing erythrocytes; the fibrous septums dividing these sinusoids contained collections of the small dark tumor cells. The hepatic architecture was generally normal; a few lobules of fat could be seen in the hepatic cells about the central vein.

Spleen: The malpighian corpuscles stood out on cut section in the usual manner; the predominant cell was the small, dark-staining type described in the myocardium. The only unusual feature about the lymphoid tissue was the concentration and uniformity of this cell type. The red pulp and the capsule appeared normal.

Pancreas: Localized collections of small, dark lymphocytes could be seen in the connective tissue about some of the pancreatic ducts. The general architecture and the composition of the glandular tissue appeared normal.

Adrenal glands: The appearance was not unusual.

Kidneys: The renal cortex had been extensively and diffusely invaded by the tumor cells; they were the same lymphocytoid cells, with dark, round nuclei and scanty cytoplasm. The infiltration of the cortex appeared recent, inasmuch as there was little or no distortion of the position of the glomeruli and tubules. The tubular epithelium in the invaded areas had a granular appearance, although the nuclei were still present; many of the lumens of the tubules contained masses of a homogeneous basophilic material.

Prostate: The structure was normal except for moderate glandular hyperplasia.

Thyroid: The tissue was normal.

Esophagus: No tumor cells were seen.

Stomach: The tunica propria was diffusely infiltrated with the previously described small, dark lymphocytes. The mucosa was highly autolyzed, so that few glandular structures could be seen.

Small intestine: This tissue was highly disorganized; the mucosal structures could not be recognized. The tunica propria was packed with lymphoid tissue, but the predominant cell type was larger and lighter staining than that in the heart and kidneys and more closely resembled the tumor cell in the biopsy specimen from the face. Peyer's patches were larger than normal, and they were packed with the small, dark, lymphocytoid cells.

Large intestine: The tissue contained circumscribed lymphatic nodules, which were large and densely packed with the small, dark tumor cells.

Lymph nodes: Sections from the lymph nodes of the neck and mediastinum showed the presence of small numbers of both types of tumor cells: the small, basophilic lymphocytes, and the large, pale reticulum cell. The sections of the nodes appeared rather inactive, as compared with the lymphoid tissue of the viscera. In none of these sections was cell division encountered that in any way resembled the mitosis in the original biopsy specimen. Figure 5 is a photomicrograph of a section from a mediastinal node.

Skeletal muscle: A section of the right sternocleidomastoid muscle showed diffuse invasion by tumor cells.

Bone marrow: The specimen from a vertebra exhibited marrow spaces filled with erythrocytes, normoblasts, myelocytes and neutrophils. The cellular composition appeared normal qualitatively, but there was some increase in the percentage of lymphoid elements. The specimen of marrow from a rib was similar to that from the vertebra.

Anatomic Diagnosis (Dr. Bruce L. Brown).—The diagnosis was lymphosarcoma, reticulum cell type, of the periorbital tissues of the right eye, with secondary

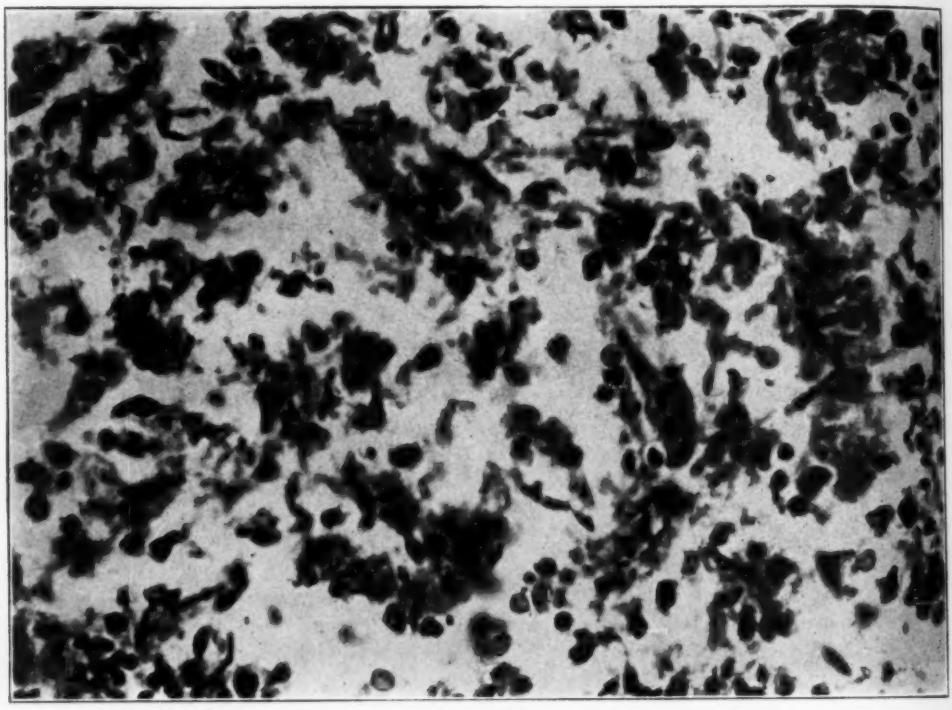

Fig. 5.—Photomicrograph of a section from a mediastinal lymph node, showing the meager involvement of the nodes.

lymphosarcomatous invasion of the lymph nodes, face, neck, heart, lungs, kidneys, liver, spleen, pancreas, stomach and large and small intestine.

Summary.—This case differed from the usual case of lymphosarcoma about the eye in a number of ways; in fact, it was characteristic in only two respects: the patient's age and sex. This neoplasm commonly occurs in the fifth decade of life and is twice as common in men as in women. The outstanding feature in this case was the time element: Only forty days elapsed from the appearance of the swelling of the lids until the patient's death; this exceedingly rapid spread from the eyelid to involve all the viscera is unusual. The early clinical

picture was confused by the presence of a foreign body and conjunctivitis in the eye, which preceded the swelling of the lid by twenty days; after hospitalization, the swelling was thought to be inflammatory until the time of the biopsy. The blood picture was not typical. Lymphocytosis is seen in a majority of cases of lymphosarcoma, but in the present case the white cell count was increased, with a normal differential count. Leukocytopenia was found on the last day of life, but this was attributed to the course of nitrogen mustard therapy. Anemia is another expected finding, especially late in the disease; in this case, however, the red cell count and the hemoglobin level continued to be fairly good to the end. A peculiarity in the behavior of this tumor was the meager involvement of the lymph nodes; lymphosarcoma, whether of nodal or extranodal origin, almost always invades the main lymph node chains secondarily; in this case the pathologic involvement of the nodes was minimal. The presence of both lymphocytes and reticulum cells in the various lesions appears contradictory, but this was seen in 25 per cent of the series of Gall and Mallory [13]; the occasional transition from one form to another emphasizes the close relation of the lymphocytic and reticulum cell type.

COMMENT

Incidence.—Lymphosarcoma arising in the eyelid is an uncommon tumor of the eye. Sugarbaker and Craver [14] analyzed 196 cases of lymphosarcoma in 1940, a twenty year collection from the tumor clinic of the Memorial Hospital for the Treatment of Cancer and Allied Diseases (all diagnoses were confirmed by biopsy); they found 1 case of primary lesion in the eyelid (0.5 per cent). Gall and Mallory [13] studied 618 cases of lymphoid tumors, a twenty year collection in the pathologic laboratory at the Massachusetts General Hospital; they also described 1 case of lymphosarcoma in the eyelid. McGavic,[15] in 1943, reported 21 cases of lymphomatoid disease involving the eye and its adnexa from the collection in the pathologic laboratory of the Institute of Ophthalmology. In this series, 17 tumors were lymphosarcomas with primary foci in the region of the eye; 3 of these tumors arose from the eyelids, and another involved the lid and orbit.

13. Gall, E. A., and Mallory, T. B.: Malignant Lymphoma: A Clinico-Pathologic Survey of Six Hundred and Eighteen Cases, Am. J. Path. **18**:381-430, 1942.

14. Sugarbaker, E. D., and Craver, L. F.: Lymphosarcoma: A Study of One Hundred and Ninety-Six Cases with Biopsy, J. A. M. A. **115**:17-22 (July 6); 112-117 (July 13) 1940.

15. McGavic, J. S.: Lymphomatoid Diseases Involving the Eye and Its Adnexa, Arch. Ophth. **30**:179-189 (Aug.) 1943.

Classification.—Proof that the term "reticulum cell lymphosarcoma" does not mean the same thing to every one is seen in the reports of the incidence of this type, for whereas Warren and Picena [16] found reticulum cell tumor in only 3.6 per cent of 308 cases, Sugarbaker and Craver [14] reported the reticulum cell type in 94 per cent of 196 cases. The terminology is so varied that any author, to be understood, must first carefully define his own terms. The terms most commonly employed today are (1) lymphocytic cell type, (2) reticulum cell type, (3) giant follicle type and (4) an undifferentiated type, to designate those tumors too poorly differentiated for classification. However, Gall and Mallory [13] subdivided their reticulum cell tumors into "stem cell lymphomas" and "clasmocytic lymphomas" and also differentiated "lymphoblastic lymphomas" from "lymphocytic lymphomas." This would appear to be an overclassification of such closely related neoplasms. One of the obstacles to uniformity in classification is the belief that argentaffin reticulum fibrils, so often seen in tumors of lymphoid tissue, are necessary to the diagnosis of the reticulum cell type; Rados [11] stated that the reticulum network is a pathognomonic feature of this type of tumor. In the Presbyterian Hospital, lymphosarcomas are designated as lymphocytic cell type when the predominant cell is small, being slightly larger than a small lymphocyte, and as reticulum cell type when the predominant cell is larger than this, usually twice as large as a lymphocyte, or even larger. The giant follicle tumors are characterized by the formation of follicles larger than is ever seen in any benign lymphomatous process. Little or no attention is paid to the presence or absence of reticulum fibers.

Prognosis.—Most authorities agree that the prognosis is poor for the patient with a lymphosarcoma. Sugarbaker and Craver [14] reported a five year survival rate of 15.9 per cent, with 10.6 per cent of the survivors free from symptoms after the five years. Stout [17] studied 218 cases of lymphosarcoma and reported a five year survival rate of 16.5 per cent, with 10.5 per cent of all patients apparently cured after five years. Of the treated patients, he found 21.8 per cent alive after five years, and 14.8 per cent were free from symptoms at the end of the five year period; when the follow-up period was extended to ten years, Stout found 14.6 per cent of the treated patients alive and 12.5 per cent free from symptoms. Of the untreated patients, 1, or 2.4 per cent, survived for the ten years, but at that time he possessed an obvious tumor. In their large series, Gall and Mallory [13] found that

16. Warren, S., and Picena, J. P.: Reticulum Cell Sarcoma of Lymph Nodes, Am. J. Path. **17**:385-394, 1941.

17. Stout, A. P.: Is Lymphosarcoma Curable? J. A. M. A. **118**:968-970 (March 21) 1942.

their mean figure for survival was 2.0 years for the entire series; the only type of lymphosarcoma for which the mean survival rate differed significantly from this figure was the giant follicle type, for which they established the mean rate of 5.0 years. In McGavic's [15] series of 17 patients with lymphosarcoma primary about the eye, 11 patients were alive and symptom free at the end of four years; 4 were alive with tumor, and 2 had died. Approximate though any comparison must be, from McGavic's cases and those of Sugarbaker and Craver; Stout, and Gall and Mallory, it would appear that lymphosarcomas of the orbital region are considerably less malignant than those found elsewhere.

Treatment.—That there is no highly successful form of curative therapy is obvious from the survival figures just cited. It is generally agreed that untreated patients with lymphosarcoma seldom live longer than two years. Lymphosarcoma is very radiosensitive, however, and it is not at all unusual to see a bulky tumor disappear after a few days of irradiation. The results have generally been so dramatic and so superior to surgical measures that it has become almost automatic to prescribe roentgen radiation as soon as the diagnosis is made. Irradiation has even been used as a therapeutic test in establishing the diagnosis. However, evidence has been accumulated indicating that the beneficial effects of radiation are temporary. Unquestionably, there have been amelioration of symptoms and disappearance of superficial tumors, but acceptable statistical evidence that the average duration of life has been prolonged cannot be found. A new, and as yet unproved, measure in the treatment of lymphosarcoma is intravenous chemotherapy with the 2-chloroethyl amines, or nitrogen mustards.[18] Dramatic results against lymphosarcoma in the terminal stage have been reported by Goodman and associates [19] in several cases: Not only the reduction or disappearance of the lymphosarcomatous masses but also improvement in appetite, strength and weight; reduction of fever, and a new sense of well-being were observed. In general, these chemicals appear to have the same effect on lymphoid tissues as does radiation; whether they have any advantage over the use of radiation is not known at present, although they have been found effective in patients who have become resistant to roentgen radiation. The response of the tumor in the subject of this report was certainly dramatic, but the clinical response was unfortunate. Surgery, as a therapeutic measure, has nearly been abandoned, probably because most patients have spread-

18. Gilman, A., and Philips, F. S.: The Biological Actions and Therapeutic Applications of the β-Chloroethyl Amines and Sulfides, Science **103**:409-415, 1946.

19. Goodman, L. S.; Wintrobe, M. M.; Dameshek, W.; Goodman, M. J.; Gilman, A., and McLennan, M. T.: Nitrogen Mustard Therapy, J. A. M. A. **132**:126-132 (Sept. 26) 1946.

ing lesions when first seen. Gall and Mallory,[13] however, reported an average survival of 7.0 years for a group of 23 patients who had radical operation; 10 of these patients survived an average of 6.6 years after operation without evidence of recurrence, and 13 patients survived an average of 5.7 years before evidence of recurrence appeared. Although this series is too small to offer conclusive evidence, the results appear to compare favorably with those obtained with irradiation. When one considers that lymphosarcoma about the eye tends to remain localized for some time, and weighs the danger of radiation to the eye, local excision of circumscribed tumors appears to be the procedure of choice for the ophthalmologist. If one finds evidence of further infiltration at the time of operation, the excision can be followed by irradiation of that area.

Dr. Algernon B. Reese and Dr. A. P. Stout made the diagrams of the type of tumor in this case, and Dr. Reese gave me permission to report the case.

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INFECTION OF THE CORNEA DUE TO HERPES SIMPLEX

An Experimental Study

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ALL HERPETIC eruptions, with the exception of those of the virus of herpes zoster, are believed to be due to the same virus. The terms herpes simplex virus, herpes febrilis virus and herpes virus refer to the same agent.[1] The commonest site of the herpetic lesion is on the lips, and the condition is therefore commonly referred to as herpes labialis. The genitals are not uncommonly involved in this type of lesion, and the eruption is then known as herpes genitalis. Aphthous stomatitis is frequently due to the herpes virus. Herpes cornealis is encountered frequently by the ophthalmologist in the form of herpetic or dendritic ulcer. The lesions of herpes tend to be recurrent, and some persons seem particularly predisposed to recurrent attacks. Frequently the lesions recur at the site of the primary lesion.

GENERAL CONSIDERATIONS

PROPERTIES OF THE VIRUS

Inoculation of human skin with vesicle fluid from any of the herpetic vesicles except those of herpes zoster results in a crop of typical vesicles of herpes simplex.[2] Similar inoculation of the scarified rabbit cornea produces keratitis of the herpetic type.[3] Herpes cornealis yields a characteristic lesion on animal inoculation. Labial herpes will produce a typical herpetic lesion on the human cornea.[4] Blanc and Caminopetros [5] passed typical lesions from herpes genitalis to the rabbit cornea and then to man. Von Sallmann [6] poduced typical corneal lesions in rabbits from herpes-infected brain. He also passed the infection from the rabbit to the human cornea. The herpetic lesions occurring with the various febrile diseases yield a virus with the same characteristics as that

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1. Van Rooyen, C. E., and Rhodes, A. J.: Virus Diseases of Man, London, Oxford University Press, 1940, p. 148.
2. Teissier, P., and others: Compt. rend. Soc. de biol. **87**:648, 1922.
3. Grüter, W.: Klin. Monatsbl. f. Augenh. **65**:398, 1920.
4. Fuchs, A.: Brit. J. Ophth. **17**:193, 1933. Löwenstein, A.: Klin. Monatsbl. f. Augenh. **64**:15, 1920.
5. Blanc, G., and Caminopetros, J.: Compt. rend. Soc. de biol. **84**:859, 1921.
6. von Sallmann, L.: Ztschr. f. Augenh. **46**:217, 1921.

obtained from primary herpes.[7] Lipschütz [8] reported that the intranuclear inclusion bodies of human herpes febrilis, herpes cornealis and herpes genitalis were indistinguishable.

THE CORNEAL LESION

The corneal lesion is characterized by the formation of minute opacities of the epithelium, which may lead to vesiculation and necrosis and the ultimate typical picture of the dendritic ulcer. The infection may accompany herpetic lesions in other parts of the body, i. e., the lips, genitalia or skin, or may occur locally in the eye. The disease appears at all ages but is very common in childhood, before the age of 10, and is more prevalent in males.[9] It is usually unilateral but may involve both eyes. There is a decided tendency to recurrence.

CLINICAL PICTURE

The clinical picture is variable. The usual onset is acute, with pain in the eye, associated with the appearance of a haze of fine granular spots in the epithelium. This is associated with a fine bedewing of the epithelium and the development of cracks and fissures, surrounded by closely packed punctate opacities. The lesion may assume a form similar to superficial punctate keratitis or dendritic keratitis. The epithelium in the region of the lesion may lie loosely on Bowman's membrane and may be brushed away. This process is known as epitheliolysis. The appearance, therefore, is one of fine epithelial opacities, which may be followed by vesicles, under which the stroma reveals a fine haze. Vesicles are rarely seen, for soon after formation they desquamate and leave faintly clouded pits, which cause pain because the interepithelial nerve fibrillae are exposed. The vesicles are usually intraepithelial. The process may persist as such for several days or weeks and finally clear up, leaving no trace. The lesions, however, may spread and coalesce to form an irregular ulcer, the dendritic ulcer. This lesion has a characteristic appearance, as it is formed by a confluence of minute herpetic lesions in an irregular, zigzag line, with many side branchings, the ends of which have beadlike nodes. The line of ulcerations rarely exceeds 1 mm. in breadth; it shows fine furrows and is surrounded by a swollen, overhanging edge and a hazy area of infiltration. The ulcer stains readily with fluorescein, but the stain rapidly diffuses under the

7. Teissier, P., and others: Compt. rend. Soc. de biol. **86**:73, 1922.

8. Lipschütz, B.: Wien. med. Wchnschr. **71**:231, 1921; Dermat. Wchnschr. **73**:798, 1921; Arch. f. Dermat. u. Syph. **136**:428, 1921.

9. Gundersen, T.: Herpes Corneae, with Special Reference to Its Treatment with Strong Solution of Iodine, Arch. Ophth. **15**:225 (Feb.) 1936.

loose adjacent epithelium.[10] Reuss [11] beautifully demonstrated the lesion by first staining with fluorescein, allowing the green stain to diffuse, and then instilling methylene blue, which stains the actual ulcerated area deep blue.

At any time during its development the process may recede and complete healing may take place without leaving scars. Occasionally the branching processes coalesce and form lobulated, shallow ulcers. Several unconnected foci may be seen, each composed of a many branched ulcer, arranged in rosettes or in star-shaped fashion. The condition is then frequently known as stellate keratitis. Should secondary infection set in, the process may spread rapidly, with disastrous results. Rarely, even in the absence of secondary infection, there occurs a deep parenchymatous spread of the process. A circumscribed opacity develops in the stroma, and the disease is known as disciform keratitis. Grüter,[12] Gundersen [9] and others were able to isolate the herpes virus from such lesions. The process may persist for many months and ultimately clear, leaving only a faint opacification or fine, scattered facets. There may be evidence of mild iritis, with multiple recurrent extravasations.[10] Doerr and Vochting, cited by Lloyd,[13] found that the virus entered the aqueous but did not penetrate into the vitreous.

In all herpetic involvement of the cornea there is hypesthesia. In cases in which this is extreme there may develop, after the herpetic process has cleared, a condition known as keratitis metaherpetica. Here, in contradistinction to the dendritic or stellate figures, are seen small, round or oval ulcers with sinuous or scalloped borders. Gundersen [9] was unable to demonstrate the herpes virus in these lesions, and it is believed that they are of neuropathic origin.[10]

HISTOLOGIC FEATURES OF THE CORNEAL LESION

Histologically, the lesions show characteristic changes involving the entire thickness of the corneal epithelium.[14] Primarily, the nuclei become hypertrophic, and the nuclear membrane is wrinkled and thickened. The chromatin becomes agglutinated and aggregated near the membrane, and acidophilic Lipschütz corpuscles enlarge, assume a polymorphic character and appear in the nucleus. The nucleus undergoes degeneration, and diffuse necrosis develops, with swelling and vacuolation of the cells. Finally, the cornea may become completely denuded

10. Duke-Elder, W. S.: Text-Book of Ophthalmology, St. Louis, C. V. Mosby Company, 1938, vol. 2.

11. Reuss, V.: Am. J. Ophth. **78**:297, 1911.

12. Grüter, W.: Ber. ü. d. Versamml. d. deutsch. ophth. Gesellsch. **48**:319, 1930.

13. Lloyd, R. J.: Am. J. Ophth. **14**:601, 1931.

14. Lloyd.[13] Fuchs.[4]

of epithelium in areas, or there may remain a thin layer of flat cells surrounded by thickened, proliferated epithelium, which shows nuclear degeneration. The necrosis may involve Bowman's membrane and spread to the superficial layers of the stroma, which may show leukocytic infiltration.

The relation of the herpetic infection to the corneal nerves is not fully understood. Grüter [15] observed early in experimental herpetic keratitis that there were swelling and proliferation of both fine and large varicose nerve nodes. He described the appearance as similar to the main body of a branching coral.

Other investigators did not substantiate these observations. Löwenstein [16] could not demonstrate an affinity of the virus for fine nerve branches in the cat or rabbit. Nakajima [17] thought he demonstrated with the slit lamp and with vital staining irregular thickening of the nerves. This was not verified by other observers. Reiser [18] could find no uniform pathologic process in the nerve parenchyma. He observed that only in later stages of the keratitis were there pathologic lesions of the larger nerve fibers. He noted only an occasional single nerve trunk involved. He expresesd the belief that the loss of sensitivity could not be attributed to these lesions but that the infiltration of cells around the fibers of the finer nerves caused damage to them and thereby produced hypesthesia. Reiser [18] observed dense accumulation of leukocytes at the limbus and marked dilatation of the lymph vessels. These congested lymph vessels were seen only in close approximation to the nerve trunks. He also noted leukocytes in perineural loose connective tissue at the limbus. He contended that the loss of corneal sensitivity was mechanical, rather than due to direct involvement of the nerves themselves.

SYMPTOMS

The symptoms are variable. Usually the onset is acute, with mild pain, lacrimation, photophobia and supraorbital neuralgia. The corneal sensitivity is reduced, and this is especially pronounced in the involved areas. A quiescent stage, with intermittent irritation and photophobia, follows the acute onset.

THE IMMUNE REACTION TO HERPES

The prevalence of recurrent attacks of herpetic lesions in man suggests that the infection did not result in significant immunity. Numerous workers have found appreciably high titers of specific antibody in

15. Grüter, W.: Ber. ü. d. Versamml. d. deutsch. ophth. Gesellsch. **50**:223, 1934.

16. Löwenstein, A.: München. med. Wchnschr. **50**:769, 1919.

17. Nakajima, M.: Zentralbl. f. Ophth. **24**:483, 1931.

18. Reiser, K. A.: Arch. f. Ophth. **139**:118, 1938; **141**:339, 1939.

the blood stream. Brain [19] postulated that the herpes virus stimulates an antibody response in the body and that when the antibody content falls below a certain level active herpetic lesions occur. With the titrated egg membrane technic, Burnet and Lush [20] found that if antibody was present at all it occurred in high titer.

Gallardo [21] observed that herpes-neutralizing antibodies were not found early in cases of the primary attack of dendritic keratitis. Sixteen to eighteen days after onset of the disease the blood showed definite neutralizing power against the herpes virus. In recurrent dendritic lesions the antibodies were present from the onset.

Active hyperimmunity results from repeated intradermal injections of herpes virus.[22] Such serum has a favorable effect in preventing herpetic infection if given prophylactically.[23] Passive immunity has been conferred on mice, guinea pigs and rabbits.

Gildemeister and Herzberg [24] found a relation between herpes and vaccinia on the basis of cross immunity tests carried out in vivo and in vitro. They demonstrated that smallpox-immune rabbits exhibited only mild reactions on injection of herpes virus. Perdrau,[25] Bedson and Bland [26] and several others were unable to corroborate these observations. They could not demonstrate any relation between the two viruses, and immunity to either infection conferred no protection against the other.

There is little evidence to support any relation between the virus of herpes simplex and that of herpes zoster. Clinically, the course of herpes zoster is more prolonged, and the bullae are considerably larger than the small vesicles of herpes simplex. Herpes zoster occurs frequently on the trunk along the distribution of a nerve, whereas herpes simplex is usually seen at a mucocutaneous junction. The vesicles of herpes zoster are subepithelial, while those of herpes simplex are intraepithelial. Pain is a predominant feature of herpes zoster, and herpes simplex is relatively painless. There is rarely a recurrence of herpes zoster, but herpes febrilis is notorious for its recurrences. The characteristic lesions of herpes simplex cannot be produced with the

19. Brain, R. T.: Brit. M. J. **2**:1064, 1937.

20. Burnet, F. M., and Lush, D.: Lancet **1**:629, 1939.

21. Gallardo, E.: Primary Herpes Simplex Keratitis: Clinical and Experimental Study, Arch. Ophth. **30**:217 (Aug.) 1943.

22. Zinsser, H., and Tang, F. F.: J. Exper. Med. **44**:21, 1926.

23. (*a*) Burnet, F. M., and Lush, D.: J. Path. & Bact. **49**:241, 1939. (*b*) Bedson, S. P., and Crawford, G. J.: Brit. J. Exper. Path. **8**:138, 1927. (*c*) Zinsser and Tang.[22]

24. Gildemeister, E., and Herzberg, K.: Deutsche. med. Wchnschr. **51**:1647, 1925.

25. Perdrau, J. R.: J. Path. & Bact. **31**:17, 1928.

26. Bedson, S. P., and Bland, J. O. W.: Brit. J. Exper. Path. **9**:174, 1928.

virus of herpes zoster. However, both viruses are thought to spread by way of the nerves, and changes have been recorded in the gasserian ganglion in cases of herpes simplex and herpes zoster.[27] Teague and Goodpasture [28] produced an eruption with herpes simplex with a zoster-like distribution. Immunologic reactions lend little support to any relationship between the two viruses. Luger and Lauda [29] found that corneal inoculation with the fluid of zoster vesicles induced no immunity to subsequent inoculation with the fluid of herpes simplex vesicles. Netter and Urbain [30] found that complement fixation does not occur between zoster antigen and anti-herpes-simplex serum.

TREATMENT OF CORNEAL LESIONS

The treatment *par excellence* of herpes cornealis has yet to be found. The predisposition to recurrence and the possibility of development of disciform keratitis make this disease a major problem in ophthalmology. The problem has been attacked from many angles, and many workers have been encouraged by their results, but few therapeutic procedures have proved their value.

The frequent occurrence of herpetic lesions in association with malaria led some early investigators to believe that the lesion was due to toxins generated by the malarial infection. They therefore advocated the use of quinine. This form of therapy remained popular for many years, especially in countries where malaria is endemic. As recently as 1936, Selinger [31] advocated its use for this and other lesions of the cornea, chiefly because of the bactericidal and astringent action of quinine.

Lloyd [13] advocated constant patching of the herpes-infected eye and the use of radiant heat to the open eye. He recommends the "thermolite" or infra-red lamp held at a distance of 20 inches (50 cm.) from the eye, the skin of the lids and face being protected with towels, for periods of fifteen minutes three times a day. Hamilton [32] asserted that heat is directly contraindicated in any form in treatment of herpes of the cornea. It is his contention that the lesion follows pyrexia and therefore heat is to be avoided but that ice compresses are to be substituted. Fever therapy is strongly contraindicated, as it is not uncommon to see labial herpes, and occasionally corneal infection, associated with this form of therapy.

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27. Howard, W. T.: Am. J. M. Sc. **130**:1012, 1905.
28. Teague, O., and Goodpasture, E. W.: J. M. Research **44**:185, 1932.
29. Luger, A., and Lauda, E.: Ztschr. f. Hyg. u. Infektionskr. **94**:206, 1921.
30. Netter, A., and Urbain, A.: Compt. rend. Soc. de biol. **90**:461, 1924.
31. Selinger, E.: Treatment of Dendritic Keratitis with Quinine Bisulfate, Arch. Ophth. **17**:1085 (June) 1937.
32. Hamilton, J. B.: Brit. J. Ophth. **27**:80, 1943.

Ultraviolet radiation has been used by some workers, with variable results. Duke-Elder [10] at one time thought this treatment of value but later decided that it was ineffective. Gundersen reported in 1936 that the virus of herpes cornealis could not be destroyed by any exposure to ultraviolet light that would be practical to use on the human eye.[9]

Darier recommended roentgen irradiation of the cornea for herpetic infection. Kumer and von Sallmann [33] found that even doses three times as strong as those usually recommended for the cornea had no beneficial effect in this condition.

Di Marzio [34] and Berud [35] both advocated the use of roentgen radiation. Di Marzio used 20 to 30 per cent of an erythema dose, and Berud repeated 8 per cent of an erythema dose four times directly to the cornea.

The postulation that the ever popular focus of infection plays an important role in corneal herpes has not withstood the test of time. Post [36] stated that all foci must be eradicated in treatment of herpes cornealis. Shapiro and Coles [37] reported a case of protracted dendritic keratitis that failed to respond until infected teeth were removed. Schwartz [38] in a series of 11 cases, reported the presence of definite foci of infection and marked improvement with their removal. Other workers have not substantiated this belief in infection as a causal agent.

Vitamin therapy has been recommended for corneal herpes. Nitzulescu and Triandaf [39] reported favorable responses of herpetic keratitis to use of vitamin B complex in large doses. Baird and Clay [40] emphasized the importance of vitamin A in the healing of all corneal ulcers, including herpes. Holden and Molloy [41] inactivated in vitro minimal doses of the herpes virus with synthetic ascorbic acid. Large doses had no effect in vivo in rabbits.

The advent of the sulfonamide drugs offered new possibilities in the therapy of herpetic infection of the eye. Kleefeld [42] stated the belief that sulfanilamide was of definite value, both therapeutically and prophylactically, in preventing recurrences of herpetic lesions. Barter [43] found

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33. Kumer, L., and von Sallmann, L.: Die Radiumbehandlung in der Augenheilkunde, Rome, J. Springer, 1929, p. 130.
34. di Marzio, Q., and Salvatori, G.: Saggi di oftal. **5**:5, 1929.
35. Berud: Klin. Monatsbl. f. Augenh. **83**:818, 1929.
36. Post, M. H.: Am. J. Ophth. **12**:885, 1929.
37. Shapiro, E., and Coles, H. D.: J. Am. Dent. A. **27**:205, 1940.
38. Schwartz, F. O.: Am. J. Ophth. **26**:394, 1943.
39. Nitzulescu, J., and Triandaf, E.: Brit. J. Ophth. **21**:654, 1937.
40. Baird, M., and Clay, G. E.: South. M. J. **33**:396, 1940.
41. Holden, M., and Molloy, E.: J. Immunol. **33**:251, 1937.
42. Kleefeld, G.: Bull. Soc. belge d'opht. **76**:14, 1938.
43. Barter, G. A.: Herpetic Keratitis, Tr. Ophth. Soc. U. Kingdom **61**:274, 1941.

no beneficial effects from the sulfonamide drugs in treatment of herpes. Improvement in 2 cases with sulfanilamide was reported by Thygeson and Stone,[44] but they postulated that the sulfonamide compounds are probably of no real value in herpetic infections. This belief is based on the knowledge that the sulfonamide drugs are known to be ineffective against all typical viruses. Chamberlain and Bronson[45] treated a number of patients with herpetic keratitis occurring as a complication of malaria. They reported significant responses to treatment with the use of sulfadiazine powder twice daily in the affected eyes.

The somewhat radical, but as yet most promising, treatment of herpetic infection of the cornea is the application of drugs directly to the cornea which destroy the infected epithelium. The postulated intranuclear location of the virus may account for the failure of most drugs. The only way that the majority of drugs could possibly act in such an infection would, therefore, be the destruction of the cell itself. Roggenkämper[46] and Kronenberg[47] advocated cauterization of the corneal epithelium with ether. The entire corneal epithelium must be briskly rubbed with a cotton applicator well soaked with ether. Other workers have not proved these results.

Hamilton[32] reported good results in the treatment of herpetic keratitis with the use of 2 per cent silver nitrate applied to the lids and conjunctival sac and directly to the corneal lesion with a cotton applicator. He also used pure phenol directly on the cornea, with satisfactory results, but stated that this radical form of treatment is unwarranted when adequate, and less dangerous, silver nitrate therapy is available.

Trichloroacetic acid, 50 per cent, and merbromin paste were recommended by Gifford[48] as cauterizing agents to be used directly on the cornea.

Probably the most satisfactory and most widely used cauterizing agent for corneal herpes is the strong solution of iodine. Gundersen[9] made an extensive clinical and experimental study of this condition. The author employed such therapeutic agents as alcohol, potassium iodide, hydrogen peroxide, epinephrine hydrochloride, curettage, alkalis, vaccination, paracentesis of the anterior chamber and ultraviolet radiation. The conclusions of Gundersen were that 7 per cent iodine and 5 per cent potassium iodide in alcoholic solution applied directly to the

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44. Thygeson, P., and Stone, W.: New York State J. Med. **43**:15, 1943.

45. Chamberlain, W. P., Jr., and Bronson, L. H., Jr.: Herpes Simplex Keratitis in Malaria, Arch. Ophth. **33**:177 (March) 1945.

46. Roggenkämper: Klin. Monatsbl. f. Augenh. **101**:285, 1938.

47. Kronenberg, B.: Treatment of Herpetic Keratitis with Ether, Arch. Ophth. **26**:247 (Aug.) 1941.

48. Gifford, S., in Brumer, V.: Ocular Therapeutics, Lancashire, England, Victor Optical Company, 1929, p. 258.

whole cornea, with resultant denuding of the entire surface, offered by far the most satisfactory results.

Eperon [49] advocated the use of 20 per cent zinc sulfate to cauterize serpiginous ulcers. This prompted von Sallmann and Lindner [50] to use a similar solution as a cauterizing agent in the Second University Eye Department in Vienna. The results were encouraging.

Iontophoresis of iodides was recommended by Verrey [51] for disciform keratitis, to clear the cornea and relieve pain. This effect has not been substantiated by other workers. Schnyder [49] used a weak solution of zinc sulfate by iontophoresis, 1 milliampere for thirty seconds, in cases of herpes of the cornea. For disciform keratitis he used a solution of iodine chloride. He claimed good results in both conditions.

Zinc sulfate, 0.25 to 0.33 + per cent, was given by Karbowsky [52] by iontophoresis for dendritic keratitis, with good results. Itoh-Yaeji [53] and Klaczko [54] also recommended this form of therapy.

Fisher [55] reported marked improvement in recurrent cutaneous herpes with weekly injections of 1:3,000 dilution of moccasin snake venom. Kelly [56] found moccasin snake venom of no value therapeutically in experimental herpes in rabbits. Its value in treatment of herpes cornealis is undetermined.

Methenamine [57] has been found to give a specific response in cases of herpes simplex on oral and parenteral administration. Buscacca [58] used this drug in treatment of herpetic lesions of the cornea but was unable to prove that this was the specific therapy for the condition.

The possibility of immunization against herpes simplex has been approached from different angles. Gundersen [9] vaccinated 8 patients with dendritic keratitis with cowpox vaccine in the usual manner, on the arm or leg, without appreciable effect on the keratitis. Four of the patients vaccinated had recurrences of the ocular lesions within two years. However, Davis [59] reported good results in recurrent herpes with repeated vaccination every ten to fourteen days with the vaccinia virus.

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49. Schnyder, W. F.: Klin. Monatsbl. f. Augenh. **63**:433, 1919.
50. von Sallmann, L., and Lindner, C.: Personal communication to the author.
51. Verrey: Bull. et mém. Soc. franç. d. opht. **48**:99, 1935.
52. Karbowsky, M.: Ophthalmologica **97**:166, 1939.
53. Itoh-Yaeji: Acta soc. opht., Japan, no. 37, 1933.
54. Klaczko, M.: Soviet. wiest. oftal., 1932, no. 1.
55. Fisher, A. A.: Treatment of Herpes Simplex with Moccasin Snake, Arch. Dermat. & Syph. **43**:444 (March) 1941.
56. Kelly, R. J.: Treatment of Herpes Simplex with Moccasin Venom, Arch. Dermat. & Syph. **38**:599 (Oct.) 1938.
57. Jaeger, K. H.: Methenamine in Virus Diseases, abstracted, J. A. M. A. **116**:260 (Jan. 18) 1941.
58. Buscacca, A.: An. argent. de oftal. **3**:3, 1942.
59. Davis, P. L.: Recurrent Herpes of the Cornea and Recurrent Herpetic Fever, J. A. M. A. **114**:2098 (May 25) 1940.

Gundersen [9] also attempted to produce higher immunity to herpes by vaccination of the lips with the virus from the patient's own dendritic lesions. He was unable to produce labial lesions, and the corneal lesions were unaffected. Other observers have reported encouraging results in recurrent herpes with repeated vaccination of skin with herpes virus [60] treated wth dilute solution of formaldehyde U. S. P.

THE ANTIBIOTICS AND VIRUS DISEASES

It has been generally accepted that as a whole the antibiotics have so far proved unsuccessful in combating virus diseases. However, there have appeared in the literature a few reports of beneficial effects, some startling, on some virus diseases. Analysis of these reports for the most part reveals that only the atypical viruses have responded.

Ornithosis has been found clinically and experimentally to be susceptible to penicillin. Turgasen [61] and Ford and Kisport [62] reported excellent results in the therapy of human ornithosis with penicillin. Heilman and Herrell [63] found that the disease was 88 per cent fatal in untreated mice but in mice receiving 1,000 units of penicillin daily only 5 per cent died.

Psittacosis of pigeon origin was also found by Heilman and Herrell [64] to be 100 per cent fatal in untreated rats, but in animals treated with penicillin a mortality of only 8 per cent was observed. The virus was not eradicated by the drug, but the animals were so protected that the majority withstood the infection.

Trachoma has been reported by Sorsby,[65] Gilford [66] and others to be highly susceptible to penicillin by local and systemic application. Keyes [67] had negative results in 1 case. The preliminary report of Darius [68] on 12 cases of trachoma treated with penicillin was inconclusive. While his results were encouraging, he did not find penicillin superior to the already established sulfanilamide therapy.

Sorsby [65] also obtained encouraging results in inclusion blennorrhea with penicillin.

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60. Robinson, H. J., and Molitor, H.: J. Pharmacol. & Exper. Therap. **74**:75, 1942.

61. Turgasen, F. E.: Human Ornithosis Treated with Penicillin, J. A. M. A. **126**:1150 (Dec. 30) 1944.

62. Ford, J. L., and Kisport, R. W.: Wisconsin M. J. **44**:491, 1945.

63. Heilman, F. R., and Herrell, W. E.: Proc. Staff Meet., Mayo Clin. **19**:57, 1944.

64. Heilman, F. R., and Herrell, W. E.: Proc. Staff Meet., Mayo Clin. **19**:204, 1944.

65. Sorsby, A.: Brit. J. Ophth. **29**:511, 1945.

66. Gilford, G. H.: Brit. M. J. **6**:232, 1945.

67. Keyes, J. E. L.: Penicillin in Ophthalmology, J. A. M. A. **126**:610 (Nov. 4) 1944.

68. Darius, D. A.: Am. J. Ophth. **28**:1007, 1945.

Tyrothricin was recommended by Parker Heath [69] for dendritic keratitis, to be used by local instillation in the eye of a 0.5 per cent solution. Milner [70] found penicillin without effect in cases of disciform keratitis.

Except for these few scattered reports of success with the antibiotics, most clinical and experimental studies have proved unsuccessful. The Naval Laboratory Research Unit No. 1 [71] tested penicillin and tyrothricin as well as tyrocidine, gramicidin, subtilin and several sulfonamide drugs and acridines, and found that none of these substances were effective in protecting mice against the influenza virus. Robinson [72] also found penicillin entirely ineffective against virus PR8 of epidemic influenza. Rabies [73] and scrub typhus [74] were also unaffected by penicillin.

PRESENT INVESTIGATION

It was the primary purpose of these experiments to determine the effect of penicillin, streptomycin and tyrothricin on the virus of herpes simplex, with special reference to its manifestations in the eye. The study was carried further in an attempt to corroborate or disprove some of the other advocated therapeutic measures. Cauterization with iodine and zinc sulfate, iontophoresis of zinc sulfate and sodium iodide, intravenous administration of sodium iodide and experiments with hyperimmune serum were carried out.

Technic.—White Swiss mice, weighing 8 to 10 Gm., were used for mouse passage. An injection of 0.02 cc. of emulsified infected mouse brain was made into the right cerebral hemisphere after first preparing the skin with 7 per cent alcoholic solution of iodine. A 27 gage needle and a tuberculin syringe were used for injection. The brains of dead or acutely ill mice were removed in toto after killing the animals by breaking the neck. Before removing the brain, the skin of the entire head was thoroughly prepared with 7 per cent alcoholic solution of iodine and 70 per cent alcohol. The skin was dissected with sterile instruments from the entire upper half of the skull. The exposed skull was then sterilized with iodine and alcohol, and with sterile instruments the cranial vault was dissected away, leaving the brain exposed. The brain was severed from the spinal cord and lifted from the skull to sterile containers. Brains to be kept were placed in sterile test tubes in a solution of 50 per cent glycerin, covered with paraffin and placed in the freezing unit of the refrigerator. Brains to be used for mouse or rabbit inoculation were emulsified in 2 cc. sterile iostonic solution of sodium chloride in glass tissue grinders, and the emulsion as such was used for inoculation.

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69. Heath, P.: Chemotherapy in Ophthalmology, J. A. M. A. **124**:152 (Jan. 15) 1944.

70. Milner, J. G.: Brit. M. J. **7**:175, 1944.

71. Personnel of Naval Laboratory Research Unit No. 1: Attempts to Protect Against Influenza Virus with Various Sulfonamides, Acridines, and Antibiotics, Science **98**:348, 1943.

72. Robinson, H. J.: J. Pharmacol. & Exper. Therap. **77**:70, 1943.

73. Martin, H. L.: Arizona Med. **1**:323, 1944.

74. Robbins, B. H.: Proc. Soc. Exper. Biol. & Med. **57**:215, 1944.

Adult chinchilla rabbits were used for corneal inoculation. The eyes to be inoculated were anesthetized by instillation of drops of 0.1 per cent dibucaine ("nupercaine") hydrochloride, repeated about four times at intervals of thirty seconds, and the injection of 0.1 cc. of dibucaine hydrochloride under the insertion of the superior rectus muscle. The superior rectus muscle was then grasped with a forceps, and with a Graefe knife three vertical incisions were made in the cornea, the blade penetrating the superficial stroma. Emulsified infected mouse brain was dropped on the cornea and into the conjunctival sac and the eye gently massaged with the lids. Both eyes were inoculated at the same time, one to be used for treatment and the other as a control. In all rabbits inoculated it was possible, at the end of twenty-four hours, to detect minimal herpetic lesions along the scarifications of the cornea by examination with the slit lamp. Within forty-eight hours typical branching dendritic lesions were manifested.

The brains were checked at periodic intervals for evidence of bacterial contamination by inoculation of blood agar plates and incubation for seventy-two hours at 37 C. At no time was evidence of bacterial contamination elicited with this technic.

The strain of virus used in these experiments was obtained from J. J., a 13 year old boy with recurrent dendritic keratitis. Material was obtained from two large herpetic vesicles, one on the lower lid and the other on the upper lip, and from the infected cornea. Serum from the vesicles was aspirated with a 27 gage needle in a tuberculin syringe, 0.02 cc. being obtained from one vesicle and 0.03 cc. from the other. The vesicle fluid was diluted with 0.1 cc. of isotonic sodium chloride solution U. S. P. and inoculated (0.02 cc.) into the right cerebral hemispheres of two groups of 3 mice each. At the end of forty-eight hours all the mice evidenced signs of encephalitis. This was manifested by humped backs, ruffled fur, irritability and occasional convulsions. Within seventy-two hours all but 1 of the mice in each group were dead, and the living mouse was moribund. The living mouse was killed, and the brains of all mice were removed for storage or further passage.

With the patient under general anesthesia, the entire epithelium of the infected eye of J. J. was curetted and the material obtained from the curettage diluted with 0.1 cc. of isotonic sodium chloride solution U. S. P. This material was inoculated into the scarified right eye of a rabbit. Twenty-four hours later there was faint punctate staining along the edges of the scarifications of the rabbit cornea. At the end of a second twenty-four hour period the picture was one of typical dendritic ulcer. The ulcer healed spontaneously in a period of thirteen days.

To determine the virulence of the strain of virus being tested, four groups of 6 mice each were inoculated by successive passage. In three of the four groups there developed fatal encephalitis within three to five days. One mouse in the third group remained well and at no time demonstrated evidence of encephalitis. It can, therefore, be presumed that this strain was fatal to at least three fourths of the type mice being tested.[75]

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75. Andervont [79b] tested two strains of herpes virus in mice to determine their pathogenicity. In his series, 50 per cent of the mice tested had fatal encephalitis, and 80 per cent showed evidence of the disease. He was unable to demonstrate any change in the characteristics or nature of the virus after thirty passages of one strain and seventy-five passages of the other. The virus maintained its corneal affinity after this number of passages through mice.

Corneal inoculation of this strain of virus resulted in dendritic lesions, which were usually manifested within twenty-four hours. Occasionally at the end of this period no corneal lesions other than those produced by the scarification were seen. However, within forty-eight hours all the 30 rabbits inoculated revealed evidence of infection. The dendritic processes started in the region of the scarifications and spread in zigzag manner. As the infection progressed, isolated ulcers appeared at the periphery and in clear cornea away from the scarifications. In untreated eyes the lesions progressed for seven to nine days and then gradually subsided, and in most cases there was no further staining of the cornea after fourteen to twenty days. In some cases a superficial infiltration of the cornea persisted for several weeks, but this usually cleared, leaving only evidence of faint scarring.

The progress of the dendritic lesions was followed by staining the ulcers with 2 per cent fluorescein sodium.

Results.—The experimental observations are presented under the individual headings of the therapeutic agent used.

PENICILLIN

One cubic centimeter of emulsion of herpes-infected mouse brain was thoroughly mixed with 1 cc. of isotonic sodium chloride solution U. S. P. containing 20,000 units of penicillin per cubic centimeter. This solution was refrigerated for eight hours and the mixture shaken at frequent intervals to prevent precipitation of the brain tissue. At the end of eight hours the solution was taken from the refrigerator and allowed to warm to room temperature. Nine mice received intracerebral injections into the right cerebral hemisphere of 0.02 cc. of the solution, each mouse thereby receiving 200 units of penicillin with the injection. Immediately after the inoculation the mice became excited, and some exhibited convulsions and 3 died. Six mice withstood the primary reaction and after several hours appeared to have fully recovered.[76] Six control mice were given 0.02 cc. of emulsified infected mouse brain by injection. Four other controls were given intracerebral injections by the same technic of 100, 200, 300 and 400 units, respectively, of penicillin in isotonic solution of sodium chloride. All mice receiving intracerebral injections of penicillin exhibited the same type of reaction, i. e., intense excitement, irritability and convulsions. The mouse receiving 100 units of penicillin withstood the injection poorly and died within twelve hours. The others receiving penicillin alone survived and exhibited no other untoward effects after the primary reaction, which lasted only a few hours. All controls receiving emulsified infected brain

76. Russell and Beck (Lancet **1**:497, 1945) demonstrated that concentrated solution of penicillin applied directly to rabbit brain produces localized necrosis in the area so treated. Walker and Johnson (Convulsive Factor in Commercial Penicillin, Arch. Surg. **50**:69 [Feb.] 1945) found that intracortical injection of penicillin in man and animals resulted in convulsions.

tissue died within three to five days, of encephalitis. The 6 mice receiving the mixture of penicillin and infected brain emulsion had encephalitis and died within four days. The brains of several mice receiving herpes virus and penicillin were removed and emulsified and reinoculated in 6 mice. Typical herpes encephalitis developed in these mice, and they died within three to five days. A group of 6 mice were inoculated by the usual technic and at the time of inoculation were given 500 units of penicillin intraperitoneally. The intraperitoneal injections of the same dose were repeated at twelve hour intervals. The course of the infection was in no way altered.

STREPTOMYCIN

Streptomycin was tested in vivo and in vitro in mice. One cubic centimeter of emulsion of herpes-infected mouse brain was thoroughly mixed with 1 cc. of solution of streptomycin containing 20,000 units per cubic centimeter. The solution was refrigerated for eight hours and shaken at frequent intervals to assure proper mixing. At the end of the eight hour period the solution was removed from the refrigerator and allowed to warm to room temperature. Six mice were inoculated intracerebrally with 0.02 cc. of this emulsion by the usual technic. Each mouse thereby received 200 units of streptomycin intracerebrally. All mice so treated became excited and hyperirritable and had convulsions, and 1 mouse died. Six control mice were given injections of the same herpes-infected emulsion as that used with the experimental mice, without the streptomycin. Three mice were given intracerebral injections of 200, 400 and 600 units of streptomycin, respectively. These mice immediately after injection became hyperexcitable and had convulsions, but shortly after the immediate reaction revealed no other untoward effects. All mice receiving the emulsion of infected brain plus streptomycin had encephalitis and died. However, these mice did not manifest signs of encephalitis before the third day, and 1 mouse survived for seven days and another for seven and a half days. Most of the controls manifested the disease before the third day, and all were dead in five days. Mice inoculated with the brains of those mice receiving herpes and streptomycin had herpes encephalitis and died within five days.

Fifteen mice were inoculated with herpes-infected emulsion. At the time of inoculation 6 mice were given 1,000 units of streptomycin intraperitoneally. This was followed by daily intraperitoneal injections of 1,000 units of streptomycin in two divided doses. Six mice of this group also received 1,000 units of streptomycin intraperitoneally in two divided doses, but treatment was not started until eighteen hours after inoculation. The remaining 3 mice were kept as controls. Three healthy mice were given daily intraperitoneal injections of 1,000 units of strepto-

mycin in two divided doses. All infected mice receiving streptomycin died within four days. One control survived until the fifth day, the others having succumbed within four days. The 3 healthy mice receiving streptomycin survived and exhibited no untoward effects after receiving 1,000 units of the drug for five days.

TYROTHRICIN

Tyrothricin, because of its known toxicity by parenteral administration,[77] was used only locally in the infected rabbit eye.

Both eyes of a rabbit were inoculated in the usual manner, with resultant infection manifested twenty-four hours later. A solution of tyrothricin, 33 mg. per hundred cubic centimeters, as recommended for ophthalmic therapy, was used, the treatment being started twenty-four hours after inoculation. The left eye was treated, and the right eye was left untreated as a control. Drops were instilled hourly for three doses, then every two hours for three doses and then four times a day. The dendritic ulcer spread much more rapidly in the treated eye. At the end of four days the treated eye was intensely injected, with intense swelling of the lids and conjunctiva. The cornea was deeply infiltrated, and almost the entire surface stained with fluorescein. The untreated eye was moderately injected, and the cornea revealed a rather extensive dendritic ulcer. The rabbit showed evidence of encephalitis at the end of five days and was therefore killed. A second rabbit was inoculated in similar manner. Six hours after inoculation, treatment of the right eye was started with tyrothricin, 33 mg. per hundred cubic centimeters. Drops were given hourly for three doses, then every three hours for three doses and then twice daily. Here, again, the treated eye reacted unfavorably. At the end of twenty-four hours both eyes showed evidence of early dendritic ulcers, but the treated eye was more inflamed, the conjunctiva chemotic and the cornea cloudy. Treatment was continued, and at the end of fourteen days the untreated eye had healed completely, whereas the treated eye still had a large ulcer and deep infiltration of the cornea.

To determine the effect of tyrothricin in a dilution of 33 mg. per hundred cubic centimeters on the normal rabbit eye, treatment was given to a healthy rabbit eye every hour for three doses, then every three hours for three doses and then twice a day. The healthy eye thus treated showed only slight hyperemia of the conjunctiva after six days of this treatment.[78]

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77. Rammelkamp, C. H., and Weinstein, L.: Proc. Soc. Exper. Biol. & Med. **48**:211, 1941. Robinson and Molitor.[60]

78. In view of the seemingly unfavorable results and the shortage of animal material, further experiments with tyrothricin were not carried out.

IMMUNE SERUM

It has been shown that active immunity is readily established in animals infected with herpes virus and that ainmals can be protected passively with prophylactic injections of immune serum.[79] In the present study an attempt was made to treat established herpetic corneal infection in rabbit eyes with herpetic immune serum. According to the technic of Bedson and Crawford,[23b] 5 rabbits recovered from corneal lesions were inoculated intradermally every five days for four inoculations to stimulate a hyperimmune response. At the end of twenty-five days these rabbits were bled by withdrawing blood from the heart, and the serum was extracted by allowing the blood to clot and drawing off the serum. The serum was pooled and refrigerated.

Two rabbits were inoculated intracorneally by the usual technic. Twenty-four hours later beginning dendritic lesions were observed. At this time, and daily thereafter, both rabbits were given intravenous injections of 5 cc. of the pooled serum. In 1 rabbit there appeared to be a favorable response, for at the end of five days the dendritic lesions appeared to be subsiding. However, despite continued treatment, after two days the lesions again started to spread and eventually involved almost the entire cornea. The lesions were still manifest at the end of fifteen days. The second rabbit ran the usual progressive course of the dendritic ulcer, which at the end of seven days began to subside. The ulcers had healed completely at the end of twelve days.[80]

SODIUM IODIDE

The reports of Thygeson [81] on intravenous injection of sodium iodide in treatment of human dendritic keratitis prompted an experimental study of this drug in an attempt to prove or to disprove its value.

The first experiment was to determine the effect of intravenous administration of sodium iodide on herpes encephalitis in mice. The dose of the drug to be used was arbitrary. According to the "Handbook of Experimental Pharmacology," [82] 0.8 Gm. of sodium iodide per kilogram of body weight proved toxic to rabbits. Dogs tolerate 0.02 to 0.03 Gm. per kilogram of body weight. It was decided to administer one tenth of the toxic rabbit dose in proportionate amounts to mice. As the drug was to be administered intravenously, it was necessary to use larger mice, so that the injection could be made into the tail vein.

79. (*a*) Perdrau, J. R.: Brit. J. Exper. Path. **6**:41, 1925. (*b*) Andervont, H. B.: J. Inject. Dis. **45**:366, 1929. (*c*) Flexner, S., and Amoss, H. L.: J. Exper. Med. **41**:357, 1925.

80. Because of shortage of animal material, attempt was not made to ascertain immune antigen titers.

81. Thygeson, P.: Personal communication to the author.

82. Bürg-Bern, E.: Handbuch der experimentellen Pharmakologie, Berlin, Julius Springer, 1927, p. 276.

Mice weighing 20 Gm. were used, and the daily dose of sodium iodide was calculated to be 2 mg.

Six mice each weighing 20 Gm. were inoculated intracerebrally with 0.02 cc. of infected brain emulsion in the usual way. At the time of inoculation and daily thereafter the mice were given intravenously 2 mg. of sodium iodide. By the end of three days all but 1 of the mice had evidence of encephalitis and were dead in five days. The living mouse at no time showed evidence of infection, and reinoculation resulted in encephalitis and death, indicating no immunity and, undoubtedly, no infection after the first inoculation. Three normal mice daily receiving 2 mg. of sodium iodide intravenously manifested no ill effects at the end of five days.

In the usual manner, both eyes of a rabbit were inoculated with herpes virus, and in twenty-four hours dendritic lesions were manifested. Beginning twenty-four hours after inoculation, 5 cc. of 10 per cent solution of sodium iodide was given daily by way of the ear vein. The corneal lesions became progressively worse, and at the end of eight days 1 rabbit died of herpes encephalitis. The corneal lesion spread, and deep infiltration became so severe in a second rabbit that the animal was killed on the ninth day. The lesions showed no tendency to heal in the third rabbit, and the animal died of herpes encephalitis at the end of ten days.

Iontophoresis of sodium iodide for disciform keratitis was recommended by Karbowsky.[52] An attempt was made to determine the effect of this treatment on dendritic keratitis in rabbits. The technic of iontophoresis as recommended by von Sallmann[83] was employed. The modified van Heuven tube as cathode was placed on the cornea, the rim fitting the limbus and being filled with a 1 per cent solution of sodium iodide. The anode was held on the back of the rabbit's head, which had been shaved. The application was employed for five minutes at 2 milliamperes of galvanic current with local anesthesia induced with 0.1 per cent dibucaine hydrochloride. Eighteen hours after treatment the eye showed considerably greater inflammatory reaction and more extensive corneal involvement than the untreated eye. The treatment was repeated after eighteen hours at 2 milliamperes for three minutes, and again in six hours. The treated eye reacted badly. There was profuse discharge, the lids were swollen and the conjunctiva was chemotic; and there was a large, deep-staining ulcer of the cornea. The untreated eye showed a typical dendritic ulcer of moderate severity. Treatment was discontinued in this eye, and two cathode iontophoretic treatments at twenty-four hour intervals with 1 per cent sodium iodide for three minutes at 2 milliamperes were given to the previously untreated eye.

83. von Sallmann, L.: Am. J. Ophth. **25**:1292, 1942.

Here, again, the reaction was unfavorable, as the eye became intensely inflamed, the dendritic ulcer spread rapidly and the cornea became deeply infiltrated. All treatment of both eyes was discontinued and the ulcers healed within three weeks, leaving dense central leukomas. The experiment was repeated on 2 more rabbits, but the iontophoresis was continued for only two minutes at 2 milliamperes of current. In 1 rabbit the treated eye reacted unfavorably and the lesions spread more rapidly and the infiltration was deeper and more extensive than in the untreated eye. The third rabbit tolerated the treatment considerably better. There were slightly greater spread of the lesions and slightly more infiltration of the stroma. The untreated eye was completely healed in twelve days and the treated eye in thirteen days.

IODINE

Gundersen [9] found that cauterization of the entire corneal epithelium with 7 per cent iodine and 3 per cent potassium iodide the most satisfactory method of treatment for human dendritic ulcer. Experimentally he found that the treatment was poorly tolerated by the rabbit cornea. An attempt in this study was made to determine the effect of a weaker solution of iodine on the herpetic lesion of the rabbit cornea. Five rabbits were tested in this series. Forty-eight hours was allowed to elapse between the time of inoculation and the institution of treatment. In each rabbit only one eye was treated, the other being kept as a control. All treatment was done with the animal under dibucaine anesthesia, and an alcoholic solution of 3.5 per cent iodine was used as a cauterizing agent. Immediately after the administration of iodine to the eye 70 per cent alcohol was applied to neutralize the action of the iodine. The eyes were then copiously irrigated with isotonic sodium chloride solution U. S. P. In 2 rabbits only the existing dendritic lesions on the cornea were treated. The lesion was briskly rubbed with 3.5 per cent iodine on a cotton applicator and then the region touched with alcohol and the eye irrigated with saline solution. Twenty-four hours later the areas treated were found to be completely denuded of epithelium and the underlying stroma densely infiltrated. Fresh dendritic lesions appeared in previously clear cornea, and as they were noted they were touched with iodine. The lesions continued to spread, and the denuded areas were deeply infiltrated and very slow in epithelizing. Healing was definitely retarded in the treated eyes, and the scarring was much more extensive than in the untreated eye.

In the other 3 rabbits of this series forty-eight hours after inoculation the entire cornea was briskly rubbed with 3.5 per cent iodine and alcohol and then irrigated, with the result that the entire cornea was denuded of epithelium. The treated eyes showed much more inflammatory reaction, and the cornea became densely infiltrated. The

untreated eyes healed within fourteen to fifteen days, while healing was delayed until twenty-eight to thirty-five days in the treated eyes and these eyes were left with dense central leukomas.

ZINC SULFATE

Zinc has had widespread use in ophthalmology. It has been used in concentrated solution as a cauterizing agent [50] and in weak solution by iontophoresis.[84] The latter method was used clinically by von Sallmann, with unsatisfactory results.[72] Schnyder and Karbowski recommended the use of 0.25 to 0.33 + per cent solution by anode iontophoresis. Both the methods were tested experimentally.

A rabbit was inoculated in the usual manner in both eyes. Twenty-four hours later typical dendritic lesions were observed. With dibucaine anesthesia, zinc sulfate, 0.25 per cent, was given by iontophoresis for two minutes at 2 milliamperes. As it was desired to drive the zinc ions into the cornea, the anode was employed on the eye and the cathode on the shaved head of the rabbit. Twenty-four hours later the entire cornea was denuded of epithelium and the stroma deeply infiltrated. Healing was greatly retarded, for the untreated eye healed within fourteen days, whereas the treated eye did not heal for twenty-one days and the eye was left with a dense corneal scar. Because of the unfavorable clinical reports of von Sallmann and the poor experimental result in 1 rabbit, to save animal material the experiment was not repeated.

A series of experiments were carried out with the use of 20 per cent zinc sulfate as a cauterizing agent on the infected rabbit cornea. Seven rabbits were tested in this series. Both eyes were inoculated, one to be treated, the other to be kept as a control. The eyes were treated in twenty-four hours in 3 rabbits, but not for forty-eight hours in the remaining 4 animals, as their lesions were minimal.

Three rabbits received extensive treatment to one eye. The eyes were anesthetized with dibucaine and the dendritic lesions stained with fluorescein. Zinc sulfate, 20 per cent, was applied liberally to the lesions and to the surrounding corneal epithelium. The zinc sulfate was well rubbed into the epithelium, and the eyes were then irrigated with isotonic sodium chloride solution. The following day the eyes were again stained with fluorescein, and the cornea was found to be denuded in the treated areas. One eye revealed a few fresh dendritic lesions, and these were again treated with 20 per cent zinc sulfate immediately. A second rabbit revealed fresh lesions in the treated eye four days after the original treatment, and these areas were again treated. The results of these treatments were as follows: The rabbit receiving the second treatment

84. Karbowsky.[32] Schnyder.[49]

after four days revealed no evidence of staining lesions in the treated eye nine days after the original inoculation. The untreated eye did not heal until the thirteenth day. In the rabbit receiving the second treatment on the following day the treated eye did not heal until after twenty-five days, whereas the untreated eye healed within fifteen days. The rabbit receiving only the original treatment had healing of both eyes on the fifteenth day.

The other 4 rabbits received treatment with 20 per cent zinc sulfate only to the localized dendritic lesions. The eyes were anesthetized with dibucaine and then stained with fluorescein to demonstrate the lesion on the cornea. A pointed applicator tightly wound with cotton was dipped in 20 per cent zinc sulfate and squeezed almost dry, so that only the localized lesions themselves were cauterized with the solution. The applicator was rubbed firmly into the epithelium. The following day the eyes were again stained with fluorescein and examined. The area immediately surrounding the treated area was denuded of epithelium and stained deeply. It was necessary to treat 2 eyes again because of fresh lesions which occurred three days after the original treatment in 1 eye and on the first and second day in the other eye. The other 2 rabbits showed no evidence of recurrence after the original treatment. In all 4 of these rabbits the treated eyes healed appreciably sooner than the untreated controls. The eye requiring the treatment to be repeated twice was healed in ten days and the control eye in fourteen days. The other eye requiring repetition of treatment was healed in ten days and the control eye in eighteen days. In the other 2 rabbits the treated eyes healed in fourteen and fifteen days, whereas the untreated controls did not heal until the nineteenth and twenty-first days, respectively. The treatment with 20 per cent zinc sulfate was fairly well tolerated by the rabbit eyes. After treatment there were denuding of the epithelium in the treated area and slight infiltration of the stroma, which cleared with the healing of the eye.

Of the 7 rabbits treated with 20 per cent zinc sulfate, 5 showed definite improvement after the treatment. In 1 rabbit the treatment seemed to make no difference in the time required to heal the dendritic lesions. The treatment appeared to be definitely detrimental to the healing of dendritic ulcer in 1 rabbit.

COMMENT

Review of the vast literature on herpes simplex, with special reference to its manifestations in the eye, revealed that extensive studies have been made concerning the virus. While many properties are well understood, others remain obscure. The infection is prevalent and widespread and definitely recurrent. Recurrences are precipitated by a wide variety of unassociated conditions. Infection results in immunity, which is

transient or insufficient to prevent recurrences. In the human subject there apparently is no local tissue immunity.

The ocular infection of herpes simplex is sufficiently prevalent and destructive to make this a therapeutic challenge to the ophthalmologist. The problem has been attacked by many earnest workers, from a wide variety of approaches. There is no known specific therapy for the herpes virus.

The antibiotic drugs penicillin, streptomycin and tyrothricin were used experimentally in this study on animals and were found to be relatively ineffective against the herpes virus. Their powers in combating certain secondary infections cannot be denied. They cannot, however, be considered the treatment of herpetic infection of the cornea.

It has been proved that active and passive immunity can easily be established in experimental animals. However, from these tentative experiments it appears that hyperimmune serum has little therapeutic effect against the established corneal infection in rabbits.

Experiments in animals with sodium iodide given systematically and introduced into the eye by iontophoresis did not bear out the claims of its advocates.

Until a therapeutic agent that is specific for the virus of herpes simplex and is nontoxic to human tissue can be found, one must depend on measures that will destroy the organism and produce only minimal tissue damage. Probably the most widely used agent is the strong solution of iodine, which destroys the virus but in so doing cauterizes and destroys the corneal epithelium. This treatment is usually well tolerated in the human eye but is definitely contraindicated in the rabbit eye. Use of 20 per cent zinc sulfate as a cauterizing agent on the infected cornea was found to be beneficial in treatment of the experimental infection in the rabbit and to be well tolerated by the eye.

CONCLUSIONS

1. (*a*) Penicillin is ineffective in combating the virus of herpes simplex in vivo and in vitro in mice.

(*b*) Penicillin in concentrated solution is an irritant when applied locally to the brain.

2. (*a*) Streptomycin in high concentrations seems to have a slight inhibitory effect on the virus of herpes simplex in vivo. It fails, however, to destroy the virus completely.

(*b*) Systemic administration of streptomyicn has practically no effect on herpes encephalitis in mice.

(*c*) Streptomycin is an irritant when applied locally in high concentration to the brain of mice.

3. Tyrothricin in dilution of 33 mg. per hundred cubic centimeters is not a beneficial therapeutic agent, but has an unfavorable effect on herpetic infection of the eye of the rabbit.

4. Hyperimmune serum is relatively ineffective in the treatment of dendritic keratitis in rabbits.

5. Intravenous use of sodium iodide is ineffective in combating herpes encephalitis in mice and has no beneficial effect in dendritic keratitis in rabbits.

6. Cathode iontophoresis of 1 per cent solution of sodium iodide has a definitely detrimental effect on herpetic infection of the rabbit cornea.

7. Local application of 3.5 per cent iodine and 70 per cent alcohol to herpes-infected eyes of rabbits delays healing and results in greater scarring.

8. Anode iontophoresis of 0.25 per cent zinc sulfate is contraindicated in dendritic keratitis in the rabbit.

9. Cauterization of dendritic ulcers with 20 per cent zinc sulfate is of definite value in the healing of these lesions in rabbit.

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INVASION OF THE OPTIC NERVE BY RETINOBLASTOMA

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IN 1931 [1] I published the results of a microscopic study of the incidence of invasion of the optic nerve by retinoblastoma. The report was based on a series of 119 enucleated eyes containing retinoblastoma. In 53 per cent of the eyes the tumor had extended into the optic nerve beyond the lamina cribrosa. In 43 per cent of the eyes the optic nerve was not severed at operation beyond the tumor extension, and, therefore, residual tumor had been left in that portion of the nerve remaining in the orbit. Thus, in 43 per cent of the cases a recurrence in the orbit and fatal termination were to be expected unless measures were directed against the residual tumor left in the nerve at the time of operation. The globes from which these statistics were gleaned were enucleated between the years 1878 and 1929, a period of fifty-one years.

For some time I have felt that these figures are not consistent with current cases. Therefore, a similar study was made of 116 eyes enucleated between the years 1934 and 1947, covering a period of thirteen years. In this series, the tumor had extended into the optic nerve beyond the lamina cribrosa in 27 per cent, and beyond the site where the nerve was severed at operation in 8.5 per cent. Therefore, in the older series the tumor extended beyond the lamina cribrosa in 1 out of 2 eyes, and in the more recent series, in 1 out of 4 eyes (table). Earlier recognition of the lesion, more accurate differential diagnosis and prompter enucleation must account for the lower incidence of nerve invasion in the more recent series.

In the older series, of the eyes showing extension of the tumor beyond the lamina cribrosa, the nerve was severed at operation beyond the extension in only 1 out of 5, while in the more recent series this was accomplished in 2 out of 3 eyes (table). This difference must be due to the surgeon's fuller consciousness of the importance of obtaining a long nerve at operation and his closer attention to execution. In the older series the short nerves were conspicuous, averaging usually only 1 mm. or so in length, while in the more recent series the nerves were much longer.

The lower mortality figures now, as compared with those of many years ago, also reflect the earlier diagnosis and the longer optic nerve

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1. Reese, A. B.: Extension of Glioma (Retinoblastoma) into the Optic Nerve, Arch. Ophth. **5**:269-271 (Feb.) 1931.

stump obtained at the time of enucleation. Hirschberg,[2] in 1869, reported 5 per cent cures, and Wintersteiner,[3] in 1897, 13 per cent cures. The Army Institute of Pathology[4] showed approximately 50 per cent cures in 1939, based on 121 cases.

It is rare for the tumor to extend into the optic nerve beyond the lamina cribrosa for more than a few millimeters, and extremely rare for it to extend as far as 8 to 10 mm. If the tumor has extended into the nerve for a distance of approximately 10 mm., it will gain access to the subarachnoid space at the site where the central vessels leave the nerve. When the tumor reaches the subarachnoid space, it spreads rapidly to the chiasm and the brain. Occasionally the tumor reaches the subarachnoid space around the optic nerve without extending back as far as the exit of the central vessels. In 1 instance the tumor extended into the nerve sheath after passing the lamina cribrosa and spread in the subarachnoid space beyond the operative section. In 2 instances the tumor reached the optic nerve sheath without invading the nerve itself.

Extension of Retinoblastoma into Optic Nerve

	1878-1929 119 Eyes	1934 to Date 116 Eyes
Extension of tumor into optic nerve posterior to lamina cribrosa	63 eyes, or 53%	32 eyes, or 27%
Operative section of nerve beyond tumor extension.....	12 eyes, or 19% of the 63 eyes	22 eyes, or 70% of the 32 eyes

In approximately 10 per cent of the cases the tumor extended out of the globe by way of the sclera. This presupposes choroidal invasion and occurred usually by way of the emissaria in the presence of extensive growth, or in the presence of buphthalmos and its attendant distention and thinning of the scleral walls.

Tumor invasion of the nerve begins in the base of the physiologic or glaucomatous cup around the central vessels; in 3 specimens tumor cells could be seen in the lumen of one of these vessels. The tumor invaded the choroid in about 25 per cent of the cases, and the rich vascular channels here offer another entrée of cancer cells to the blood stream.

The size of the tumor in the globe does not seem to have a direct bearing on whether or not the tumor extends into the nerve. Sometimes the tumor is small and shows a nerve extension.

2. Hirschberg, J.: Anatomisch Untersuchungen über Glioma retinae, Arch. f. Ophth. **14** (pt. 2):30-102, 1868.

3. Wintersteiner, H.: Das Neuroepithelioma retinae, Vienna, Franz Deuticke, 1897.

4. Army Institute of Pathology: Personal communication to the author.

Retinoblastoma arises from the nuclear layers of the retina and is a tumor, therefore, of nerve tissue origin. It appears to have a certain affinity for invading nerve tissue, such as that of the optic nerve bundles. This happens so literally at times that the size and the shape of the bundles, surrounded by their septums, are preserved, with the tumor tissue occupying the place of the nerve fibers. The tumor has little tendency to invade fibrous tissue, as evidenced by the fact that when the optic nerve is atrophic the hypertrophied septal tissue appears to be a barrier to invasion of the nerve, and by the fact that retinoblastoma spreads through the sclera to the extraocular structures only exceptionally (10 per cent), and then late in the presence of extensive growth.

From time to time there have been advocates[5] of the combined intracranial and orbital operation for retinoblastoma.[6] It is my feeling that the rationale of this operation is based on false premises. The operation is a logical procedure, based on the available information in the literature. Unfortunately, this information is not altogether correct. Some of the advocates of this combined operation have been motivated by the figures published by me in 1931.[1] The main purpose of the present paper is to correct these figures with current cases, which show, as previously discussed, a much lower incidence of nerve extension.

Furthermore, the literature[7] states that retinoblastoma proves fatal because of intracranial extension by way of the optic nerve. On the basis of Merriam's analysis[7a] of the autopsies performed in 15 of our

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5. (*a*) Ray, B. S., and McLean, J. M.: Combined Intracranial and Orbital Operation for Retinoblastoma, Arch. Ophth. **30**:437-445 (Oct.) 1943. (*b*) Jean, G. W.: Discussion of Glioma of the Retina, ibid. **51**:505 (Sept.) 1922. (*c*) Glioma of the Optic Nerve: Correspondence, J. A. M. A. **100**:1793 (June 3) 1933. (*d*) Dott, N. M., and Meighan, S.: Intracranial Resection of the Optic Nerve in Glioma Retinae, Am. J. Ophth. **16**:59, 1933. (*e*) Rand, C. W.: Glioma of Retina: Report of a Case with Intracranial Extension, Arch. Ophth. **11**:982-994 (June) 1934. (*f*) Shannon, C. E. G.; Jaeger, R., and Forster, F. M.: The Combined Intracranial and Orbital Operation for Bilateral Retinoblastoma, Tr. Am. Ophth. Soc. **42**:326-333, 1944.

6. The accepted procedure in the combined intracranial and orbital operation for retinoblastoma is first to perform the cranial operation by excising the intracranial portion of the nerve between the chiasm and the optic foramen. The best worked-out technic has been published by Ray and McLean,[5a] and this includes coagulation of the optic nerve at the optic foramen and the insertion of a plug of muscle tissue over this site. Twelve to thirteen days later the enucleation is done, at which time the entire orbital portion of the nerve is removed, along with the globe.

7. Leber, T.: Die Geschwulstbildungen der Netzhaut, in Graefe, A., and Saemisch, T.: Handbuch der gesammten Augenheilkunde, Leipzig, Wilhelm Engelmann, 1916, vol. 7, pp. 1723-1943. Adam, C.: Statistisches, Klinisches und Anatomisches über das Glioma retinae, Ztschr. f. Augenh. **25**:330-350, 1911.

7a. Merriam, G. R.: Retinoblastoma: An Autopsy Analysis of 15 Cases, to be published.

cases of death from retinoblastoma, it appears that retinoblastoma more frequently proves fatal by distal metastases than it does by extension into the cranial cavity. In 9 of Merriam's 15 cases, or 60 per cent, there were blood-borne distal metastases—to the bones in 7 cases (46.7 per cent), to the viscera in 6 cases (40.0 per cent) and to the lymph nodes in 6 cases (40.0 per cent). In only 9 of the 15 cases had intracranial extension occurred via the optic nerve, and in 7 of these there was generalized leptomeningeal involvement. Thus it can be seen that retinoblastoma is much more than a local disease which jeopardizes life only by extension to the cranial cavity via the optic nerve.

The advocates of the combined intracranial and orbital operation must conceive of the tumor as invading the optic nerve and extending backward within the confines of the nerve to the intracranial cavity. The examination of eyes with retinoblastoma shows that the usual extension into the optic nerve proper is only for a few millimeters posterior to the lamina cribrosa, and that an extremely rare occurrence is its extension as far back as 10 mm. If the tumor extends into the nerve for approximately 10 mm., it then gains access to the subarachnoid space at the site where the central vessels make their exit from the nerve. After the tumor reaches the subarachnoid space by this route, or by direct extension from the optic nerve into the subarachnoid space, it then spreads rapidly throughout the subarachnoid space, not only of the involved optic nerve but of the chiasm and elsewhere throughout the cranium. This is the manner in which the tumor may reach the cranium, and not by extension through the substance of the optic nerve to the intracranial portion of the nerve and to the chiasm, and hence to the brain. Thus, when the tumor reaches the subarachnoid space and travels in the manner described here, an excision of the intracranial portion of the nerve will probably not be beyond the intracranial extension of the tumor.

In this recent series of 116 eyes with retinoblastoma enucleated since 1934, only 10, or 8 per cent, showed that the operative section was not beyond the tumor extension into the nerve. In all probability this figure could be lowered appreciably if the surgeon had secured an adequate portion of nerve at the time of the enucleation. It is rare indeed for the tumor to extend as far as 10 mm. into the nerve, and certainly there is no reason for an optic nerve to be shorter than 10 to 12 mm. when an eye harboring a retinoblastoma is enucleated.[8]

8. Almost any length of nerve may be secured at operation if the following procedure is practiced: Pass a heavy silk traction suture through the insertion stumps of the internal and external rectus muscles, engaging some of the adjacent sclera. When the optic nerve is cut, pull the globe forcibly outward with the traction sutures, placing the optic nerve on a stretch, and at the same time press the blades of the scissors backward along the nasal wall of the orbit.

Furthermore, if the tumor has extended into the nerve as far as 10 mm., it probably already has reached the subarachnoid space, where it spreads rapidly, and would probably be beyond the site where the nerve would be excised in the case of an intracranial operation. If, by chance, the case happens to be one in which the operative section was not made beyond the tumor extension into the nerve proper, this fact should be available within forty-eight hours if the optic nerve is prepared as biopsy material and examined microscopically.[9]

I therefore believe that, on the basis of the arguments presented in this paper, there is no justification for the combined intracranial and orbital operation for retinoblastoma.

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9. The optic nerve should be severed from the globe flush with the sclera immediately after the enucleation. Sections for microscopic study should be cut from the proximal, distal and central portions of the nerve to determine whether there has been tumor extension and, if so, whether or not the operative section has been made beyond it.

CLINICAL COURSE OF OCULAR COMPLICATIONS OF ARACHNODACTYLY

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IT IS the general belief that the dislocations of the lens and the rigid iris seen in arachnodactyly are nonprogressive, congenital defects. Observations on 21 patients over periods of five to fourteen years and on 25 others for shorter periods have convinced me that many are true abiotrophies. While some patients complain only of reduced visual acuity, others show progressive dislocation of the lens, with uveal degeneration ending in detachment of the retina. Knowledge is far from complete, and only a single eye of this type has been examined in the laboratory. This article is offered in the hope of attracting other case reports.

The disease is inherited as a dominant in many families and as a recessive in others. A parent with normal eyes and some of the skeletal defects may transmit the disease in complete form, and the same is true of a parent with normal skeleton and congenital bilateral dislocation of the lens. It is not unusual to find a parent with some of the features of the disease, a child with all the typical defects, another child with hands and feet only characteristic of the condition and other children who are normal or rather tall and thin. Isolated cases are occasionally seen, but it should be assumed that every case of bilateral congenital dislocation of the lens is one of arachnodactyly until the family has been studied thoroughly.

The arachnodactylic infant may be as plump as the normal child, with no other abnormality at the time but dislocation of the lens and abnormal flexibility of some joints. This child grows tall and very thin by the fifth year and in the teens may become very tall, but is never of the pituitary type. One such patient (E. C., among the individual cases reported) reached 6 feet 8½ inches (204.5 cm.) by the fourteenth year, and another grew from 5 feet 7½ inches (171 cm.) to 6 feet 1½ inches (187 cm.) in two and one-half years (M family). The feet are so long and narrow that difficulty is experienced in getting shoes to fit. Size 12½ AA was used by a 12 year old boy.

Read at the Eighty-Third Annual Meeting of the American Ophthalmological Society, Hot Springs, Va., June 6, 1947.

Occasionally a typical case is seen in a very short person. The father of a very tall boy was 5 feet 4½ inches (164 cm.) in height but presented typical features of the disease in every other detail, with the lenses well out of place, a defect which attracted attention to the family.

The normal broad pelvis may be found in affected female patients, with considerable subcutaneous fat on the lower portion of the torso,

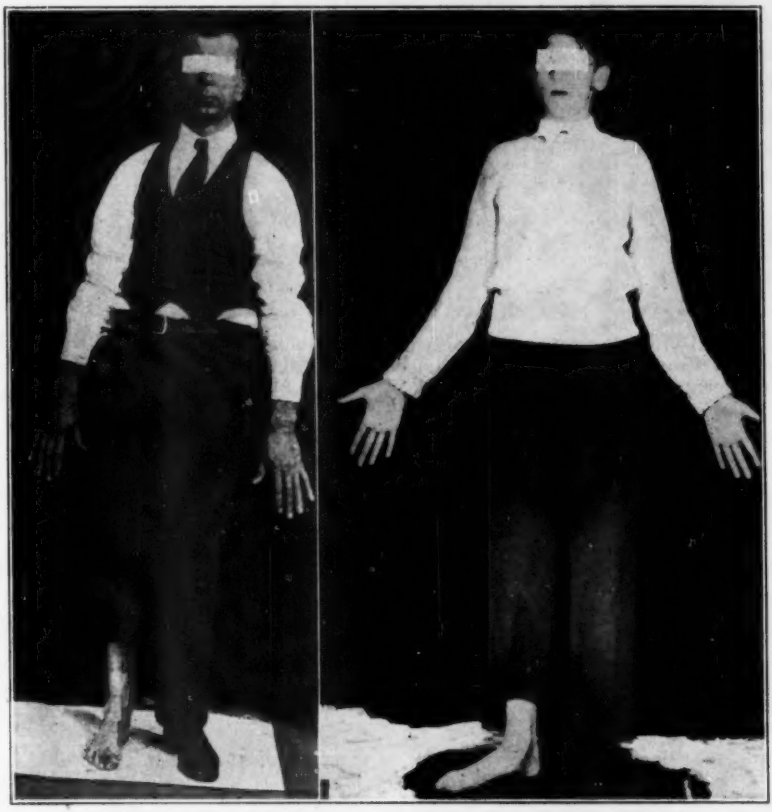

Fig. 1.—The father is 5 feet 4 inches (162.5 cm.) in height, and the son, 5 feet 7½ inches (171 cm.). The son grew 6 inches (15 cm.) in two and one-half years.

which is out of all proportion to the thin chest, narrow shoulders, long thin fingers and abnormal height. Scoliosis is common but does not appear until the teens. A tall, thin child may fill out well at puberty, and this is especially true of girls. A deep midsternal groove is seen, which in exceptional cases is so deep that the heart is displaced to the left. A transverse depression at the lower part of the thorax is probably due to traction of the diaphragm, to which the weak bony structures yield. Horner's syndrome has been reported, with a smaller breast on the same side in females and with the hooked little finger,

defects which are also seen in syringomyelia and which lead one to think that all are due to damage to the trophic nerve cells about the central canal of the spinal cord in the embryo. The span of the out-

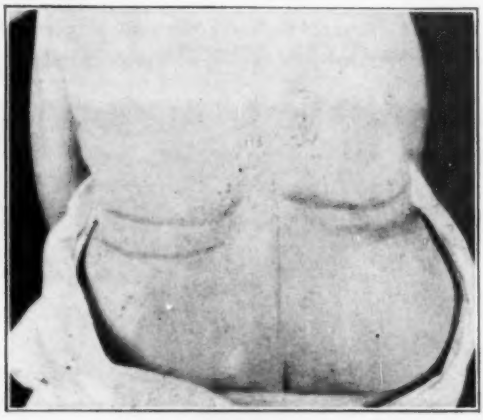

Fig. 2.—Broad, female type of pelvis and abundant subcutaneous fat on the torso of woman with arachnodactyly, bilateral dislocation of the lens and retinal detachment. The patient was referred by Dr. H. M. Gurley.

Fig. 3.—Hands and feet of patient shown in figure 2, with typical defects of arachnodactyly.

stretched arms, from one finger tip to the other, should not be more than the height, but in these patients it often exceeds the normal by several inches, resembling the normal stature of apes. Abnormal flex-

ibility of joints may be evident in infancy and is a source of entertainment among children. The skeletal changes do not usually appear until the third to the fifth year and, because of gradual development, often escape notice. When the child goes to school, the defect in vision is discovered, and the patient is brought to an oculist, who finds the dislocated lenses. The youngest child with this defect whom I have seen was 15 months old, but the defect is considered congenital. The effort to improve vision with lenses may be difficult because the child is often mentally slow or actually defective. It is easy to overlook displacement of the lens of lesser degrees unless the pupil is widely dilated to expose some part of the outline of the lens. Almost without exception, the dislocations are upward and outward. Somewhat later than normal, the patient begins to read and may acquire an education, even with vision of 10/50 in one eye. This defective vision may improve as he grows older. Despite the low visual acuity, the patient may read with little difficulty, doing it in his own way. When the child is 10 years of age, the observer can usually tell whether the defect belongs to the favorable group of congenital abnormalities or to the abiotrophies, with positive pathologic changes and a poor prognosis. Visual acuity gives a good idea of the future, as improved vision implies moderate dislocation of the lenses and absence of uveal degeneration. Children with poor vision usually have progressive displacement of the lens, associated with atrophy of the tapetum far forward, sclerosis of the choroidal vessels, opacities in the vitreous and pigment on strands of the vitreous and the suspensory ligament of the lens. The iris is aplastic, with good color and well developed pupillary margin; but the bold network on the surface, derived from the vascular capsule, is missing and the fibers are all radial. Occasionally poor vision is present without a satisfactory explanation. It has been assumed that poor vision was due to dislocation of the lenses, but there are usually other reasons, which require careful consideration before removal of the lens. Detachment of the retina occurs after slight injury, after operation or spontaneously. There has been much argument as to which operation was safest—needling or removal of the lens. Needling is difficult, and absorption is slow and incomplete. Detachment has followed removal of the lens and also has occurred spontaneously. Some surgeons use the loop to remove the lens; but if an iridectomy is done, the lens should float up into the wound without difficulty even if well out of place. If an iridectomy is not done, prolapse of the iris follows and recurs after replacement. The lens is rounder than normal because of relaxed lenticular fibers, and the specific gravity and weight are subnormal because of underdevelopment. One lens of this type (De V. family) snapped back into the

eye, with subsequent hemorrhage, an event suggesting a persistent hyaloid artery.

Cowan and Spaeth suggested iridectomy to expose a lens-free area. The results they have obtained compel serious consideration of this procedure.

It is my opinion that any operation is hazardous, because of the faulty construction and lowered vitality of the eyes of these patients, and that the type of operation is not significant.

The uveal changes have been seen in children of 10 years, but many escape notice until adult life. Atrophy of the tapetum appears first in the extreme periphery of the retina, with large clumps of pigment here and there and sclerosis of the choroidal vessels. Pigment granules can be seen on the strands of vitreous, the fibers of the suspensory ligament and even in the hyaloid fossa, if the lens has moved out. Floaters develop in the vitreous, and the lens is displaced into the anterior chamber or, more often, into the vitreous. The spastic iris atrophies, becomes rigid and will not respond to atropine. If the pupillary area is free, the slit lamp shows ragged strands of vitreous waving in and out of the pupil as the lids sweep across the eyeball. At this stage, slight accidents occasion retinal detachment, which may have existed unobserved if located far forward or if the pupil is small and the vitreous cloudy. The lens may be dislocated into the anterior chamber, and 3 eyes of 2 patients of this series were operated on for that reason. More often the lens falls back on the floor of the fundus and in time becomes opaque. If the displacement of the lens exposes a clear portion of the pupil, vision may be improved for a time. A person with arachnodactyly with lenses in normal position may show the uveal degeneration already described. It is impossible to predict the rate of progress, but in this group blindness has occurred as early as 14 years, and as late as 35 years, of age. The oldest patient with good vision in one eye was 54 years of age. The case histories are reported as family groups, together with a number of individual cases.

CASE HISTORIES [1]

DE V. FAMILY (OCTOBER 1932)

Grandfather: Not seen, but evidently the transmitter.

Father: Normal eyes; delicate bony structure with scoliosis.

Mother: Normal eyes; typical skeleton, hands and feet.

Daughter: Normal.

Son: Normal.

Daughter (aged 18): Typical complete case. Vision with correction 10/40 and 10/30. Atrophy of peripheral tapetum with clumps

1. Affected members are designated by italics.

of pigment; pigment on fibers of suspensory ligament; beginning sclerosis of choroidal vessels.

June 4, 1945: Vision with correction: perception of moving objects and 10/40; lenses dull and cloudy; irises smooth and without character; detachment far forward in right eye.

Daughter (aged 13): Typical complete case. Vision with correction 10/30 and 10/70. Pigmented, atrophic areas peripherally; sclerosis of choroidal vessels; lenses cloudy; beads of pigment on fibers of suspensory ligament.

March 2, 1943: Operation (Dr. Moehle) for retinal detachment in left eye and reoperation, without success.

Son (aged 9): Typical complete case. Vision 10/200 and 10/70 with —8.00 D. sph. Beads on fibers of suspensory ligament and strands of vitreous waving in and out of pupil; view of fundus difficult.

May 21, 1943: Removal of lens (Dr. Moehle) from right eye to improve vision; lens snapped back into eye, with hemorrhage into vitreous and loss of vision.

July 15, 1947: Right eye blind, soft and painful; ciliary injection; pupil large and fixed, with opaque, organized mass in vitreous. Left eye: Vision 8/200, not improved; lens cloudy, with only a small bit of pupil free at extreme periphery temporally.

Son (aged 5): Typical complete case. Patient did not read or cooperate; irises smooth; denses dislocated up and out.

May 31, 1945: Vision 10/200 and 10/15, with correction. Both pupils lens free; pigment on strands of vitreous and posterior corneal surfaces; advanced choroidal atrophy in both eyes, with much pigment in clumps; height 6 feet 4½ inches (194 cm.); patient wears no. 12 shoe.

Comment.—This family has been under observation fourteen years. The mother, with normal eyes but typical skeletal defects, transmitted the disease to 4 of 6 children. The uveal changes were found in all the affected children. Operation was performed on 1 child to improve vision and on another to correct retinal detachment, without success in either case.

P. FAMILY (SEPTEMBER 1935)

Mother (aged 33): Incomplete case.

R. E.: +5.50 sph. ⊃ +2.50 cyl., axis 90 = 20/20
L. E.: +7.00 sph. ⊃ +0.50 cyl., axis 30 = 20/20

Lenses in normal position; broad, female pelvis, with typical hands and feet.

Father: Normal.

Daughter (aged 9½): Typical complete case.

R. E.: +10.00 sph. ⊃ +2.00 cyl., axis 105 = 20/70
L. E.: + 8.00 sph. ⊃ +2.00 cyl., axis 75 = 20/70

Jaeger type 5 and 7 with correction.

May 1942: Vision 10/30 and 10/100 with correction. Right eye: Jaeger type 1. Left eye: Blind; lens well back in vitreous, opaque; loose strands waving in and out of pupil.

March 1944: Both lenses on floor of fundus; atrophy of tapetum, exposing pale choroidal vessels; irises atrophic.

R. E.: +9.00 sph. ⌒ +1.50 cyl., axis 90 = 20/33 (?)

L. E.: +10.00 sph. ⌒ = 10/200

July 1946: R. E.: +9.00 sph. ⌒ +1.50 cyl., axis 90 = 20/25 (?)

L. E.: +10.00 sph. = 10/100

(Contact lenses give 20/33? and 10/70)

Daughter (aged 10): July 1946: Vision normal; typical skeleton, hands and feet.

Daughter (aged 13): Normal.

Child (aged 19): Not seen.

Comment.—The transmitter (mother) has an atypical condition, but has 1 daughter with the typical disease and another with an atypical form. The condition would not have been discovered in either the mother or the second daughter if the examination of the oldest daughter had not been made and a search for other cases in the family begun. Two children escaped. The family has been under observation eleven years.

K. FAMILY (OCTOBER 1935)

Grandfather: Not examined, but from photograph and the son's statement, it would seem he had the typical disease.

Father (aged 33): Typical case.

R. E.: Vision 5/200, not improved.

L. E.: Vision 10/200; with —1.00 sph. ⌒ —6.50 cyl., axis 120 = 20/25. Right pupil partly free of lens; little displacement of left lens. Dilation showed displacement of left lens. Pigment on strands of vitreous and suspensory ligament.

January 1943: Right lens dislocated into anterior chamber; pain severe; moderate redness; tension 25 mm. (McLean). Lens removed; vision 10/40, with correction. Wound opened from within two months later. Wound reopened; flap jumped over incision. No relief from pain; anterior chamber collapsed; posterior scleral trephination; enucleation. Epithelial invasion of anterior chamber.

Mother: Normal.

Daughter: Typical case. Killed in automobile accident. Vision with correction 20/200 in each eye (Dr. Ohly's clinic).

Daughter (aged 7½): Typical case.

R. E.: —6.00 sph. = 10/40

L. E.: —5.50 sph. = 10/70

Patient walked at age of 18 months; congenital deafness; first teeth at age of 10 months.

October 1940: With correction patient reads Jaeger type 2 and 6. No changes in fundus and no deposits of pigment.

February 1942: Dr. James Smith removed left lens to improve vision; resulting vision 10/30, with ability to read Jaeger type 5 with correction. Later, detachment of retina; poor result from diathermy.

April 1945: Right lens dropped down, leaving clear pupil and vision 20/33 with +11.00 sph. ⊂ +2.00 cyl., axis 105. Vision in left eye 10/100.

Comment.—This family has been under observation twelve years. The father had typical skeletal characteristics and displaced lenses. The better eye had little displacement and no other pathologic change, with good vision. The right eye had been lost through epithelial invasion after removal of the lens. The chief complaint was pain, with no increase of tension until collapse of the chamber. Two daughters were affected. The living child had operation for improvement of vision, with fair temporary result. Later, the retina became detached and diathermy was given, without success. The father's condition was found after the daughter came to the clinic for glasses to improve vision.

M. FAMILY (JANUARY 1938)

Father (aged 45): Typical complete case, but height only 5 feet 4 inches (163 cm.) and weight 147 pounds (66.7 Kg.); wears no. 8 shoe. Vision 10/30 and 10/20 with correction. Tension 15 and 18 mm. (McLean).

May 1942: Vision 10/100 in each eye. Lenses dropped down, covering both pupils.

May 1943: Vision 10/50? in each eye; tension 25 mm. (McLean).

June 1944: R. E.: Pupil lens free; +16.00 sph. ⊂ +2.00 cyl., axis 90 = 10/15 with ability to read Jaeger type 2.

L. E.: Vision not improved.

Mother: Normal.

Son (aged 13): Typical complete case. Corrected vision 10/50 and 10/40. Height 5 feet 7 inches (170 cm.); reads Jaeger type 1 and 3 with difficulty.

May 1943: Height 6 feet 1½ inches (187 cm.); patient wears no. 11 shoe.

October 1945: Vision 10/70 and 10/40 with correction; Jaeger types 1 and 8 read with difficulty. Irises smooth and without characteristic change; no sign of uveal degeneration other than pigment on strands of vitreous. Left eye has the freer pupillary area.

Son (aged 11): Normal.

Son (aged 8): Normal.

Comment.—This family has been under observation nine years. The father was short but otherwise had typical defects. He had fair vision until the lenses dropped down; after more complete luxation, vision improved in one eye. The growth of the affected son in two and one-

half years, from 5 feet 7 inches to 6 feet 1½ inches, is noteworthy. The father's condition would have escaped notice if the son with the typical disease picture had not applied for improvement of vision.

F. FAMILY (FEBRUARY 1940)

Father (aged 51): Hypermetropic astigmatism but lenses in normal position; definite skeletal characteristics.

Mother (aged 48): Normal.

Daughter (aged 19): Normal

Daughter (aged 18): Typical complete case.

R. E.: —10.00 sph. = 5/200; Jaeger type 12 with correction.

L. E.: —10.00 sph. = 10/50.

July 1945: R. E.: —9.00 sph. = 10/200.

L. E.: —9.00 sph. = 10/50.

With reading correction, vision nil (R. E.) and Jaeger type 13 (L. E.).

Pigment attached to vitreous strands; albino fundi, hair light brown; irises smooth and without features usually present.

Son (aged 15 months): Fine, plump infant; both lenses displaced up and out.

Daughter (aged 15): Normal.

Son (aged 14): Normal.

Daughter (aged 11): Normal eyes; typical hands and feet.

Son (aged 7): Normal.

Comment.—This family has been under observation seven years. The father, with hypermetropic astigmatism and skeletal defects, transmitted the defect to one daughter in complete form, and her child, at 15 months of age, has bilateral displacement of the lens. Another daughter has normal eyes but typical hands and feet.

REPORT OF INDIVIDUAL CASES

CASE 1.—S. S., aged 17 years; typical case. Left lens removed by Dr. E. C. Place, without complications. No improvement in vision. Family not studied.

Comment.—No explanation for the poor vision was found.

CASE 2.—E. C., aged 14 years; typical case (Dr. J. H. Ohly).

January 1936: Height 6 feet 8½ inches (204.5 cm.); weight, 165 pounds (74.8 Kg.); span, 6 feet 11½ inches (212 cm.); no. 11½ shoe. Correction of + 11.00 sph. gives vision of 10/70 and perception of large objects in respective eyes. Pupils rigid; opacities in vitreous; atrophy of tapetum. Right lens cannot be found; left lens opaque, on floor of fundus; vitreous strands waving in and out of pupils. Fingers "double jointed"; spinal curvature. No family history obtained or study made.

CASE 3.—A. F., aged 6 years.

January 1936: Dislocation of lenses but bony features not pronounced.

June 1936: Dr. Irving Jacobs removed both lens from anterior chamber, with excellent results.

December 1941: Vision with correction 20/20 and 20/25; Jaeger type 1.

March 1945: Patient timid and mentally retarded. Vision with correction 20/33 in each eye. Iris atrophic; thinning of tapetum peripherally, vitreous strands waving in and out of pupils.[2]

Comment.—The only successful operations were performed in this case. Pathologic signs were present nine years after the operation.

CASE 4.—Miss E., aged 38; normal lenses but typical skeletal defects.

February 1942: Vision 20/20 with corrections of —10.00 and —9.50 sph. for the right and left eyes, respectively. Peripheral fundus showed tapetal atrophy, with choroidal vessels losing color.

October 1946: Vision with correction 20/25 in each eye.

Comment.—Uveal degeneration in a patient with normal eyes, with typical skeletal defects and myopia.

CASE 5.—Mr. S., aged 20; typical skeletal changes. Right lens normal; vision 20/20 with + 1.50 sph. ⊃ + 3.00 cyl., axis 90. Left lens down on floor of fundus, opaque; anterior chamber deep, view of fundus impossible because of small, rigid pupil and opacities in vitreous. Height, 6 feet 2½ inches (189 cm.); weight, 155 pounds (70.3 Kg.); 10½ AA shoe. Left eye lost vision, without injury or inflammation, six years ago.

Comment.—The better eye was hypermetropic, with astigmatism, but was otherwise normal. The patient has been under observation four years, with no change in his condition.

CASE 6.—Paul B. July 1937: Typical case, referred by Dr. W. M. Howard. Vision with correction 10/50 in each eye; read Jaeger type 5 when held close to eyes

December 1944: Dr. Howard reported on patient at age of 13. Vision with correction 20/50 and 20/70. Lenses had not changed position. Patient was wearing low minus astigmatic lens and was doing well at school. No other case has been found in his family.

Comment.—This case shows how well a patient with only fair vision can do at school.

SUMMARY

The ocular lesions of arachnodactyly have been regarded as malformations, but many are true abiotrophies, with progressive changes in the uvea. We have attributed the poor vision to malposition of the lens, but there are other, more serious, causes. The eyes with the more serious defects do not withstand operation or injury. In the present series, 12 operations were done on 7 eyes of 6 patients. Three operations were done on 3 eyes of 3 patients to improve vision, without attaining the object; and 1 of these eyes was operated on again for subsequent retinal detachment, without success. Eight operations were performed to save 4 eyes of 4 patients from disaster. A man

2. This case has been reported elsewhere (Am. J. Ophth. **20**:1042, 1937).

aged 40 (Mr. K.) underwent operation on the poorer eye for removal of the lens from the anterior chamber, with temporary success. Three operations followed, the last an enucleation, which the pathologist's report of "epithelial invasion of the anterior chamber" explains. A child of 6½ years was operated on by Dr. Irving Jacobs for bilateral dislocation into the anterior chamber, with an interval of six months between operations; and excellent vision resulted, the only successful outcome in the series. Another patient was operated on twice for detachment of the retina, without benefit.

In eyes with good vision the course is uneventful, as the displacement of the lens and the uveal changes are minimal and neither is progressive. The prognosis for eyes with poor vision is not good because of associated progressive changes in the uvea and the tendency to complete dislocation of the lens and retinal detachment.

Operation to improve vision should be done only after the most careful examination, as there are usually other reasons for the defective vision besides dislocation of the lens. The usual rule to operate on the poorer eye may not hold in such cases, for vision in one eye is usually very poor, even in the more favorable cases.

The ophthalmologist will be asked whether a patient with this defect should marry, but he often is not able to decide whether the heredity in a particular case is dominant or recessive.

A patient with some of the skeletal features may pass the blight in complete form to most of the children (De V family). An apparently normal person with dislocated lenses may do likewise.

Every case of bilateral congenital dislocation of the lens should be considered as one of arachnodactyly until it has been shown otherwise. Since finding the first case of this series, in 1932, I have seen but 1 case of dislocated lenses without clear evidence of arachnodactyly in the family.

DISCUSSION

Dr. Frank D. Carroll, New York: C. C. Clarke (Ectopia Lentis, Arch. Ophth. **21**: 124 [Jan.] 1939) analyzed the records of 31 patients with congenital dislocation of the lens treated at the Vanderbilt Clinic. He concluded that the best procedure in cases requiring surgical intervention was preliminary iridectomy followed by a loop extraction of the lens. This was performed on 10 eyes, without operation complications interfering with sight.

I have reviewed the records of 7 patients with arachnodactyly not previously reported. One of them was an intelligent woman in her twenties, who was over 6 feet (180 cm.) tall. Her lenses were dislocated up and nasally in each eye, and she obtained 20/30 vision with her aphakic correction. Three patients were infants treated by the pediatricians and never examined by an ophthalmologist. Two of these had congenital heart disease, which is commonly associated with arachnodactyly. The third was born with contracture of the hands,

feet and knees. This condition has improved somewhat during the past ten years, but plastic surgery will probably be necessary. Two sisters, both mentally retarded, had this syndrome. One died at the age of 6 years; the other had both lenses removed by loop extraction, and cyst of the iris developed after operation in one eye and was treated by the injection of iodine. Another patient, besides arachnodactyly and ectopia lentis, had congenital cardiovascular disease with a dissecting aneurysm, a complication previously reported in the literature, and a calcified astrocytoma in the occipital lobe. After the operation on the brain, an iridectomy was performed on the right eye. This was followed by detachment of the retina. With a high myopic correction he has useful vision in the left eye. The last patient, although only 12 years of age, had the typical appearance of patients with this syndrome; with a high myopic correction vision in her eyes is 2/200 and 20/30.

Dr. Ralph I. Lloyd, Brooklyn: Since 1932, when I became interested in this condition I have almost always been able to find positive evidence of arachnodactyly in other members of the family, and I know of but 1 case of congenital dislocation of the lenses in which there was any doubt of the occurrence of arachnodactyly in the family. If the patient has congenital dislocation of both lenses but a normal skeleton, that person can be the parent of a child with a completely typical syndrome; but the reverse is also true.

LIPEMIA RETINALIS ASSOCIATED WITH ESSENTIAL HYPERLIPEMIA

ERWIN E. GROSSMANN, M.D.
AND
JOHN B. HITZ, M.D.
MILWAUKEE

LIPEMIA retinalis was first described by Heyl [1] in 1880. The condition is known to occur in cases of hyperlipemia when the fat in the blood is sufficiently emulsified to become visible in the retinal vessels. The hyperlipemia that is associated at times with alcoholism, phosphorus poisoning, pneumonia, peritonitis and starvation has never been known to become ophthalmoscopically visible. Duke-Elder [2] underlined the statement that "diabetes is the only disease wherein the condition becomes sufficiently marked to be seen ophthalmoscopically in the retinal vessels." Duke-Elder also noted the one exception to this, the case reported by Wagener,[3] in 1922, of a 9 year old boy with leukemia who had undergone radiation treatment. Since its first description, in 1880, about 60 cases of lipemia retinalis have been reported in the literature, and it is noteworthy that all these have been of diabetic patients, usually in the younger age groups. Since in all the reported cases the patient was either approaching or in a state of coma, it has been assumed that acidosis necessarily exists. Thus, in a recent textbook, Tassman [4] expressed agreement that acidosis is apparently a factor and that the condition is seen in young diabetic patients when the lipid content of the blood rises above 5 per cent. However, Lepard,[5] reporting a case in 1936, noted that acidosis was

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1. Heyl, A. G.: Tr. Am. Ophth. Soc. **3**:54, 1880.

2. Duke-Elder, S. W.: Textbook of Ophthalmology, vol. 3, St. Louis, C. V. Mosby Company, 1941.

3. Wagener, H. P.: Am. J. Ophth. **5**:521, 1922.

4. Tassman, I. S.: The Eye Manifestations of Internal Diseases, St. Louis, C. V. Mosby Company, 1946.

5. Lepard, C. W.: Lipemia Retinalis in the Nondiabetic Patient, Arch. Ophth. **32**:37 (July) 1944.

not a factor, nor did the patient have diabetes. Holt and his co-workers [6] also reported the condition in a case in which the diagnosis of idiopathic lipemia had been made. The case of Lepard is also assumed to be one of idiopathic hyperlipemia, and both the patients were young children. Kauffman [7] in 1943 reported a case of lipemia retinalis in a man aged 25; this case he considered the fourth reported instance of the disease in a nondiabetic person, Wagener's case being the first. The diagnosis in Kauffman's case was chronic gastritis and chronic alcoholism. Although these 4 cases are the only ones reported in the ophthalmologic literature, there has been occasional reference to the retinal picture in the pediatric literature in cases of idiopathic hyperlipemia. Goodman and his co-workers,[8] describing the clinical picture of idiopathic hyperlipemia in a 1 year old child, commented that the eyegrounds were consistent with the picture of lipemia retinalis. It is noteworthy, therefore, that most of the instances of nondiabetic lipemia retinalis, uncommon as they are, were noted in association with the condition called idiopathic, or essential, hyperlipemia. This condition is primarily a pediatric disease and is probably due to a familial defect or an anomaly of lipid metabolism. Holt [6] suggested that hyperlipemia may occur in cases of hepatic disease in which conditions are such that the fat metabolism is not impaired but the internal utilization of fats is interfered with. The main change in the blood serum is the increase in the amount of the neutral fat. So far as it is known, the case to be presented represents the fifth recorded instance of lipemia retinalis seen in a nondiabetic person, and is probably the first reported case of the condition in a nondiabetic adult.

REPORT OF A CASE

A white man aged 55 was admitted to the Veterans Administration Facility because of recurring pains in the lower substernal region and epigastric "burning," which was not relieved with antacids. There was no complaint of visual disturbance. Routine physical examination revealed normal skin; no xanthomatosis; an enlarged liver, palpable 3 fingerbreadths below the costal margin; a normal spleen, and a blood pressure of 100 systolic and 60 diastolic.

Samples of blood had the appearance of a creamy emulsion. The Wassermann and Kahn reactions of the blood were negative. The fasting blood sugar, determined on three occasions, was 113, 85 and 116 mg. per hundred cubic centimeters. The glucose tolerance test gave normal results. The serum amylase was 104 mg. per hundred cubic centimeters; gastric analysis gave normal results, and the urine was negative for albumin and sugar. Roentgenograms of the chest, the long bones and the skull revealed nothing significant; the roentgenographic series of the gallbladder was normal. The electrocardiogram was normal. In marrow obtained by sternal

6. Holt, L. E.; Aylward, F. X., and Timbus, H. G.: Idiopathic Lipemia, Bull. John Hopkins Hosp. **64**:279, 1939.

7. Kauffman, M. L.: Lipemia Retinalis, Am. J. Ophth. **26**:1205, 1943.

8. Goodman, M., and others: Idiopathic Lipemia, J. Pediat. **16**:596, 1940.

puncture, an abundance of large cells was observed, the cytoplasm appearing foamy. Biopsy of the liver revealed large amounts of fat in the cells. (A detailed clinical report by the medical department will be made elsewhere.)

Vision was 20/20 in each eye, without glasses. The anterior segment was normal. The fundus revealed the typical appearance of advanced lipemia retinalis. Its general appearance was striking. The vessels, arteries and veins were flat and ribbon like. They appeared to be filled with cream. The color of the arteries was similar to that of the veins, so that the vessels in their course from the disk could not be distinguished very far out into the periphery. The light reflex was absent from the surface of the vessels. There was no perivascular infiltration. Differentiation of veins and arteries was made possible only by noting the relative difference in caliber, the veins maintaining a ratio to the arteries of 3:2. The rest of the fundus was a homogenous, pale cream color. The color of the disk appeared to be lighter but within normal limits. At this stage, analysis of the blood serum revealed that the total lipid content was 13.13 per cent and the cholesterol 1,128 mg. per hundred cubic centimeters.

The patient was then placed on a low fat diet, and within five days the fundus was noted to change from a pale cream to a light salmon color. The color of the vessels was also seen to have undergone definite changes. Examination of the vessels for a distance of 1 disk diameter from the papilla revealed that the arteries were a bright red and the veins the usual dusky, deeper hue. The light reflexes in this portion of the retina were also considered normal. The vessels peripheral to this point also showed a return to normal color, but to a much lesser degree. Although veins and arteries could be distinguished from each other, there was a notable decrease in brightness of the light reflexes, and the color was definitely less decided than that of the vessels near the disks. A sample of blood taken at this stage revealed the total lipid content to be 4.06 per cent and the cholesterol 665 mg. per hundred cubic centimeters. A few days later the sample of blood contained 2.12 per cent total lipids and 443 mg. of cholesterol per hundred cubic centimeters. Examination of the fundi at this time revealed a generalized rosy red color of the eyegrounds. The vessels appeared to be normal in color from disk to periphery. The ratio of the caliber of the veins to that of the arteries was 3.2. The light reflexes were normal, and the previous appearance of "flatness" of the vessels was absent. The low fat diet was discontinued and within five days there occurred what was called a gastric crisis, i. e., severe gastric cramps. Examination of the fundi at this time again revealed the typical textbook picture of lipemia retinalis. The fundi were seen two days before the occurrence of the gastric crisis, and at this time the peripheral portions of the vessels were much paler than normal, although the portions within 3 disk diameters of the papilla were fairly normal. The retinal condition never returned to its original textbook picture, as the patient soon learned that he felt better when he was on a low fat diet.

A sample of blood was sent to Dr. S. J. Thannhauser, of Boston, who verified the previous findings and corroborated the clinical diagnosis of idiopathic hyperlipemia. His observations are compared with the normal values in the following tabulation.

Lipid Constituents	Amount, Mg./100 Cc.	
	Patients	Normal
Neutral fat	3,440	0-150
Total phospholipids	188	180-250
Total cholesterol	550	150-200
Free cholesterol	230	40- 70
Cholesterol esters	320 (58 per cent of total)	70- 75

SUMMARY

Severe lipemia retinalis was seen in a man aged 55 whose condition was diagnosed as idiopathic hyperlipemia. At the time of his admission the blood serum revealed a fat content of 13.13 per cent. When, with a low fat diet, the blood lipid content fell to 4.06 per cent, the hyperlipemia was seen to recede. When the fat content of the blood fell to 2.12 per cent, the condition of lipemia retinalis was observed to be absent. When the patient returned to a regular diet, the blood lipids were again elevated, to 4.7 per cent, and the condition of lipemia retinalis reappeared.

CONCLUSIONS

Although acidosis may usually be associated with hyperlipemia, as noted in diabetic persons, it is not an important factor in the production of the lipemia retinalis which occurs in the condition known as idiopathic, or essential, hyperlipemia.

The condition of lipemia retinalis may occur with a normal carbohydrate metabolism.

It is noteworthy that the condition of essential hyperlipemia occurs in infants and young children. This may account for the paucity of reports in the literature concerning the fundi, as relatively few cases will have the benefit of an ophthalmologist's consultation.

It is felt that the condition known as idiopathic, or essential, hyperlipemia affords a field for the continued study of lipemia retinalis, and it is urged that all patients with such a condition be given a thorough ophthalmologic study. The case reported here is thought to be the first reported instance of essential hyperlipemia in an adult. The cause of the condition is still quite unknown.

The case presented was from the medical service of Dr. M. F. Koszalka and Dr. J. J. Levin. Dr. S. J. Thannhauser and Miss Grace Ballard, of the Mount Sinai Hospital, Milwaukee, gave assistance in the laboratory studies.

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Notes and News

GENERAL NEWS

The following lectures in ophthalmology will be delivered at the Royal College of Surgeons of England, in Lincoln's Inn Fields, London, W.C. 2, England:

Tuesday, March 29, 1949: A. Franceschetti (professor of ophthalmology, University of Geneva), "Cataract Associated with Lesions of the Skin"; G. B. Bietti (professor of clinical optics, Pavia University), "Protein and Amino Acid Deficiencies in Ophthalmology."

Wednesday, March 30, 1949: Prof. E. Hartmann, "Psychosomatic Symptoms in Ophthalmology," and H. J. M. Weve (professor of ophthalmology, Rijksuniversiteit), the subject to be announced later.

SOCIETY NEWS

Ophthalmological Society of the United Kingdom.—The annual congress will be held at the Royal Society of Medicine, 1 Wimpole Street, London, W. 1, on March 31 and April 1 and 2, 1949. The subject under consideration will be "Corneal Grafting"; the discussion will be opened by Dr. R. Townley Paton, New York; Prof. A. Franceschetti, Geneva, Switzerland; Prof. G. P. Sourdille, Nantes, France, and Mr. J. W. Tudor Thomas, Cardiff, Wales.

The rest of the program will appear later. The annual dinner will be held on March 31. For further information, apply to Mr. G. J. O. Bridgeman, 45 Lincoln's Inn Fields, London, W.C. 2, England.

Central Illinois Society of Ophthalmology and Otolaryngology.—At the meeting of the Central Illinois Society of Ophthalmology and Otolaryngology in November, the following officers were elected: president, Clifton S. Turner, M.D., Peoria, Ill.; president elect, Harold Watkins, M.D., Bloomington, Ill.; vice president, Meredith Ostrom, M.D., Rock Island, Ill., and secretary-treasurer, Philip R. McGrath, M.D., Peoria, Ill.

PERSONAL NEWS

Prof. Joseph Meller's Festschrift.—To celebrate Professor Meller's seventy-fifth birthday a collection of scientific articles is planned. As at present the number of contributions to German periodicals is necessarily limited, articles will be acceptable for the *Festschrift* which have appeared in any periodical provided the article was printed with the dedication to Dr. Meller's seventy-fifth birthday. Reprints of such original articles could then be bound in one volume and could serve as a *Festschrift*. Notice of such an article should be sent to Prof. J. Böck, Augenklinik, Graz, Austria.

Society Transactions

SOCIÉTÉ FRANÇAISE d'OPHTALMOLOGIE

Annual Meeting, May 18-22, 1947

The French Society of Ophthalmology held a successful second postwar meeting in Paris, May 18 to 22, 1947. A number of foreign ophthalmologists attended. The western hemisphere was represented by Castroviejo, of New York, and Busacca, of São Paulo, Brazil. The Belgians and Swiss were numerous, as usual. The Italians appeared on the scene again, and two Polish colleagues, Szymanski and Kapuscinski, emerged from the other side of the iron curtain. Nordenson was there and Zeeman, and, of course, Arruga. There was an important British contingent, with Law, Doggart, King, Maccallan and Mathewson, and a single ophthalmologist from Dublin.

The meetings were held every morning; in the afternoon there were operations in the Paris hospitals and visits to the Pasteur Institute and to the National Institute for the Blind. The International Council of Ophthalmology and the International Association for the Prevention of Blindness held their meetings in Paris during the same week.

On Sunday, May 18, the papers dealt mostly with adnexa of the eyes. There were two papers, by Fritz and Bonhomme, on contact lenses, and the moot subject, at least in Europe, of relations between the physician and the manufacturer of contact glasses was discussed. Guillaumat, and others, spoke on what they call "relative hemianopsia"; in some patients in whom no defect can be detected on the tangent screen there is a difference in the visual perception of two identical objects shown simultaneously in the normal and in the abnormal half of the field. In the reviewer's opinion this is akin to the phenomenon of sensory suppression of Bender and Teuber (Nystagmoid Movements and Normal Perception, *Arch. Neurol. & Psychiat.* **55:** 511-529 [May] 1946).

On Monday, May 19, papers dealt mostly with diseases of the cornea, conjunctiva and lens. Busacca gave an account of his investigations on the conjunctival lymphatics with vital injections of trypan blue. There was a long discussion on the etiology of trachoma, started by Nataf, who is one of the early champions of the role of the rickettsias; Busacca, of course, had something to say about this, but no undisputable conclusion was reached. Bietti showed some interesting photographs, taken in Rome during the war, with a German electronic microscope. One could distinctly see a number of very small round bodies; there is a possibility that these may be the agents of trachoma. Castroviejo presented two excellent colored films, one on cataract extraction and the other on corneal transplantation. There was a general and interesting discussion on the latter subject. Paufique and Sourdille are to prepare the 1948 symposium of the society on this subject. Paufique had been able to remove the eye of a patient who died of pneumonia a few months after receiving a partial, nonpenetrating transplant, and his photographs showed how the grafted tissue is accepted by the host. In cases of intracapsular cataract extraction in which the lens capsule is taut and

the forceps is unable to get a hold, Sédan makes a minute puncture in the capsule and a small amount of liquid is allowed to escape; after this the capsule forceps can get a purchase.

On Tuesday, Professor Bonnet, of Lyon, presented the annual symposium for 1947, which was devoted to ophthalmoscopic study of the fundus in diseases of the blood, such as leukemia. This study had been published in book form a few weeks earlier, as is the custom with the French Society of Ophthalmology. It is a magnificent contribution to our specialty; there are 75 illustrations in color, 47 in black, and 263 pages of text. It is not possible to present an abstract of this symposium, but a study of Bonnet's book will be found worth while.

On Tuesday evening there was the traditional dinner, with toasting and speech making. Marigot de Treigny, the secretary of the French Society of Ophthalmology, welcomed the numerous foreign members present that night, and a considerable number of the latter answered.

The papers presented on Wednesday, May 21, dealt mostly with diseases of the fundus. Franceschetti stressed the value of chorioretinitis in the diagnosis of toxoplasmosis. Fritz showed that not only the retinal arteries but also the veins are important in the diagnosis and prognosis of general diseases. Amsler, in photographs taken at different times in the same patients, was able to demonstrate that retinal hemorrhages will travel more than one suspects and that in their shift downward they will by-pass the macula. Sourdille read an excellent paper on the various types of operation for glaucoma; Weekers told of his satisfactory results with nonpenetrating cyclodiathermy in uveitis with secondary hypertension. Rouher had something to say about the treatment of retinal edema by intravenous injections of procaine. This treatment has been widely used in France in the last few years, and often successfully, particularly in cases of arterial spasm.

On the last day, Thursday, Weekers read an interesting paper on his studies of critical fusion frequency. There is a frequency threshold for the perception of a steady light, but this threshold varies with the state of the retina and of the optic nerve fibers; when they are not normal, the perception of a steady light will be possible, even with slower flashing. Weekers was able to study this on the whole surface of the field; not only is the diagram thus traced similar to that of the field mapped in the usual way, but anomalies,in early glaucoma for instance, can be detected in this way earlier than in any other. Verrey spoke of his work on the cytology of the aqueous in several diseases of the eye, and the meeting came to an end with an excellent paper by Guillaumat and Gilles on roentgenography for detection of foreign bodies in the eye, with a new and accurate method devised by Porcher.

I regret that this report of the meeting, with its fifty-seven papers and lengthy discussions, is necessarily sketchy and incomplete.

May I suggest to our American confrères that attending the meeting of the French Society of Ophthalmology in Paris in May can be both interesting and pleasant? The society has a considerable number of non-French members; there are at present 18 Americans, and many more would be welcome; finally, Paris in May is usually at its best.

E. HARTMAN.

Book Reviews

Neurosurgical Pathology. By I. Mark Scheinker, M.D. Price, $8.75. Pp. 355, with 238 illustrations. Springfield, Ill.: Charles C Thomas, Publisher, 1948.

This book is a concise, interesting and easily read presentation of the pathology of cerebral disease as it confronts the neurosurgeon. In essence, the volume consists of (1) a discussion of changes produced by trauma to the head and spinal cord, and (2) a description of the various cerebral neoplasms and their prominent clinical manifestations.

The opening chapter is devoted to the author's concept of cerebral edema and its role in producing intracranial pressure. This chapter offers the neuro-ophthalmologist much thought-provoking material and opens avenues for explanation of a number of anomalous circumstances associated with choked disk (low pressure at lumbar puncture; small tumor causing high intracranial pressure). Even those who do not subscribe entirely to the author's physiologic concepts must accept the reasonableness of the argument on the basis of present knowledge.

Pathologic changes which occur after nonpenetrating injury to the central nervous system are interpreted in terms of the concepts outlined in the third chapter. Descriptions of various entities that puzzle many ophthalmologists, such as subdural hematoma, are fully understandable.

The organization of the chapter on brain tumors is excellent. Each type of tumor is logically presented; the incidence, pathologic picture and prognosis are given, and a short clinical résumé is made. This results in easy understanding and retention of the essential characteristics of each of the many types of tumor that occur. The tumors that particularly concern the ophthalmologist, such as pituitary adenoma, suprasellar cyst, meningioma and angioma, are fully described, and their relations to the visual pathology are indicated. Cerebral abscess and hydrocephalus are discussed in the concluding chapters.

Although this book was written for the student of neurosurgery, it is of definite value to the neuro-ophthalmologist who needs a working knowledge of neurosurgical pathology. However, any ophthalmologist will be well repaid by even a few hours of study of this book.

P. J. LEINFELDER.

Das Haftglas. By Dr. E. Burki. Basel, Switzerland: S. Karger, 1948.

This book deals with the mathematical optics of contact glasses. The book is divided into two sections, a theoretic and a practical. The

latter is not so well developed as it might be and, since it is written in German, will not appeal to many practicing ophthalmologists. The theoretic section, on the other hand, is done with the usual German thoroughness. The book is recommended to those who are interested in the optics of contact glasses.

FRANCIS H. ADLER.